Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package might contain assessments and/or conclusions and recommendations written by individual FDA members. Such conclusions and recommendations do not necessarily represent the final position of the individual staff member, nor do they necessarily represent the final position of any FDA office or division. We have brought the agenda items to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to any subsequent regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all relevant internal activities have been finalized. Any final determination may be affected by issues not discussed at the advisory committee meeting.

Food and Drug Administration

Meeting of the Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

July 22-23, 2008

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MEMORANDUM

TO: Members, ACPS-CP

FROM: Helen Winkle
Director, Office of Pharmaceutical Science, CDER, FDA

DATE: June 23, 2008

RE: ACPS-CP Meeting July 22-23, 2008

Dear Committee Members and Invited Guests,

We look forward to your participation in the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting on July 22-23, 2008. The meeting will focus on a number of important science issues currently being addressed in the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER). As you know, this office is mainly focused on the review of the quality of pharmaceutical products prior to market. This includes all pharmaceutical products – small molecule and proteins, and generic versions of these products. Through your participation and advice on the advisory committee, we are able to develop and finalize our standards for reviewing and approving products and set policy for regulatory decision-making.

Our last meeting of the advisory committee was in October 2006. Since that time a number of new issues have surfaced in OPS that we will bring before the advisory committee for discussion and advice. Background materials for each of the proposed topics are attached. Since 2006, the term for a number of members has expired and new members have been appointed. We look forward to welcoming the new members and to their scientific input into the topics being brought before the committee.

We look forward to a very productive meeting in July. We value the opportunity to solicit your assistance in defining and solidifying OPS direction in developing sound, scientific responses to the emerging issues.

At the start of the meeting on July 22, I will outline the goals and objectives for our meeting and I will also provide to you a brief update on OPS ongoing initiatives and activities.

DAY 1 (July 22, 2008)

DAY 1 (Topic 1) – Nanotechnology in Drug Manufacturing, Drug Delivery, and Drug Products

This topic was first introduced as an awareness topic to the advisory committee in April 2004. Nanotechnology is a very rapidly growing area of science and technology which is currently being used in the manufacture of a number of pharmaceuticals.

CDER continues to grapple with how best to regulate these nanomaterial-containing products and whether our current regulatory requirements are adequate for the evaluation of such products now and in the future. The presentations will provide information on state-of-the-art applications of nanotechnology in the field of drug delivery, pharmaceutical product development and manufacturing. The discussion will focus on issues that need to be addressed by the FDA regarding nanomaterial-containing products, their safety, their manufacturing, and the regulatory procedures involved in the approval of such products.

Draft Questions for the Committee:

1. Is CDER guidance needed for the development of nanotechnology derived drug applications?
2. If guidance is needed from CDER, what areas should these guidances focus on?
3. In light of the many definitions of nanotechnology available, how should CDER define nanotechnology, for the purposes of guidance development?

DAY 1 (Topic 2) – Lead in Pharmaceutical Products

This is a new topic for the advisory committee. FDA is interested in assuring that we are focused on any possible issues that might be associated with lead in pharmaceuticals and that we have the appropriate regulatory framework for addressing these issues. Following a historical background and introduction of the topic, the discussion will be framed by presentations on the effects of lead exposure on human populations, information on lead levels in pharmaceutical products (as tested by FDA), compendial testing of pharmaceutical products, and the approach taken by Center for Food Safety and Nutrition (CFSAN) on lead limits set for food.

Draft Question for the Committee:

1. What additional information would be necessary for us to gather to appropriately determine the next steps?

DAY 2 (July 23, 2008)

DAY 2 (Topic 1) – Bioequivalence Methods for Locally Acting Drugs that Treat Gastrointestinal (GI) Conditions

The typical use of *in vivo* bioequivalence studies that compare pharmacokinetic parameters may not be an appropriate surrogate of pharmacological activity for locally acting drugs that are used to treat GI conditions. Selection of the most appropriate bioequivalence method requires understanding of physicochemical properties of drugs, product design, and drug product safety and efficacy profiles. After framing the topic, we will present an approach and proposal as to current thinking on the bioequivalence issues for these locally acting drugs.

Draft Questions for Committee:

1. What role should biorelevant dissolution play in developing BE recommendations for low solubility locally acting drugs that treat GI conditions?
2. What role should systemic pharmacokinetics play in developing BE recommendation for low solubility locally acting drugs that treat GI conditions?

DAY 2 (Topic 2) - Drug Classification of Orally Disintegrating Tablets (ODT)

This class of dosage forms presents a challenge with consideration to established standards on solid oral dosage forms regarding nomenclature and regulatory oversight. The topic will be introduced to the Committee to frame the issues in order to ensure that we have consistent standards for all products marketed whether as an ANDA product or an NDA product. It is hoped that the discussions will assist OPS in developing consistent standards for this class of products.

Draft Questions for Committee:

1. What properties (*in-vivo* or *in-vitro*) do you consider critical to this dosage form?
2. Should physical properties (e.g., size, formulation, and disintegration times) be a primary factor in determining conformance to this dosage form?
   a. If so, how specific or restrictive should the criteria be?
3. Can labeling (i.e., instructions for use) be considered sufficient to define the dosage form?
   a. If so, should labeling describe/include differences between/among NDA and ANDA products?
4. Are there special issues that should be considered (e.g. patient compliance, target populations/conditions)?

DAY 2 (Topic 3) – Bioequivalence Methods for Inhaled Corticosteroids

This class of drug products presents challenges to establishing bioequivalence. A study design that is sensitive to dose differences is required. As an update to the Committee, current thinking and possible study designs will be discussed. It is anticipated that in the future OGD will present research outcomes and possibly bioequivalence method recommendations for inhaled corticosteroid products.

We are looking forward to a very stimulating discussion with the committee on the selected topics. Have a safe and enjoyable journey to Rockville, MD. The meeting will be held at the Advisory Committee Conference Room (rm. 1066 on the lower level), 5630 Fishers Lane in Rockville. If you need any additional information please do not hesitate to contact Bob King (Robert.King@fda.hhs.gov).

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)

Advisors & Consultants Staff Conference Room, Rm 1066
5630 Fishers Lane, Rockville, MD 20857

JULY 22-23, 2008
(Scheduled Presentation Times May Change Due to Open Public Hearing Requirements)
TENTATIVE AGENDA
(SUBJECT TO CHANGE)

Day 1: Tuesday, July 22, 2008

8:30 a.m.	**Call to Order and Opening Remarks**	**Ken R. Morris, Ph.D.** Chair Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Designated Federal Official
8:45 a.m.	**Welcome, Introductory Remarks, and OPS Update**	
9:00 a.m.	***Topic 1: Nanotechnology in Drug Manufacturing, Drug Delivery, and Drug Products***	
10:15 a.m.	**BREAK**	
	Committee discussions and recommendations	
12:00 p.m.	**LUNCH**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	***Topic 2: Lead in Pharmaceutical Products***	
3:15 p.m.	**BREAK**	
	Committee discussions and recommendations	
5:00 p.m.	**ADJOURNMENT**	

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)

Advisors & Consultants Staff Conference Room, Rm 1066
5630 Fishers Lane, Rockville, MD 20857

JULY 22-23, 2008
(Scheduled Presentation Times May Change Due to Open Public Hearing Requirements)
TENTATIVE AGENDA
(SUBJECT TO CHANGE)

Day 2: Wednesday, July 23, 2008

8:30 a.m.	Call to Order	**Ken R. Morris, Ph.D.** Chair, ACPS-CP
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Designated Federal Official

8:45 a.m. ***Topic 1: Bioequivalence Methods for Locally Acting Drugs that Treat Gastrointestinal (GI) Conditions***

10:00 a.m. **BREAK**

Committee discussions and recommendations

12:00 p.m. **LUNCH**

1:00 p.m. Open Public Hearing

2:00 p.m. ***Topic 2: Drug Classification of Orally Disintegrating Tablets (ODT)***

Committee discussions and recommendations

3:00 p.m. **BREAK**

3:15 p.m. ***Topic 3: Use of Inhaled Corticosteroid Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products***

4:45 p.m. **Conclusion and Summary Remarks**

5:00 p.m. **ADJOURNMENT**

DAY 1 TOPIC 1:

Nanotechnology in Drug Manufacturing, Drug Delivery, and Drug Products

Background Information for the Nanotechnology Session
July 22, 2008 ACPS-CP Meeting

As CDER grapples with questions regarding how to regulate nanomaterial-containing products, several issues have surfaced, including 1) what are the types of nanotechnology applications that will be reviewed by CDER, 2) what are the unique features of these applications that may pose a scientific and/or regulatory challenge to reviewers, 3) are our current regulatory requirements adequate for the evaluation of nanomaterial-containing products and 4) what can we do to expedite the development of safe and effective nanomaterial-based pharmaceuticals.

Recognizing that nanotechnology applications in drug development are likely to have a significant impact on the products that FDA regulates, CDER has initiated a number of activities in order to evaluate how this new technology fits into the current regulatory framework. Some of these activities will be mentioned in an introductory presentation by the Office of Pharmaceutical Science.

Regardless of the definition for nanotechnology, products containing nanomaterials are being investigated for potential applications as therapeutics and some products containing nanoscale materials are already on the market. While some of these nanomaterials are nanoscale versions of larger materials used in approved products, other nanomaterials are novel and have never been used in drug products. Meanwhile, the regulatory requirements to ensure preclinical safety, quality and manufacturing processes for products containing such novel materials, are not different from those requirements for products that do not contain nanoparticles. There have been questions raised about the need for "nano"-specific requirements, in part to aid the development of products containing nanomaterials, and in part because nanomaterial containing products may need to fulfill different regulatory requirements prior to approval. Having heard the various opinions, and evaluated the state of the science, the FDA established a Nanotechnology Task Force, which issued a report in July 2007. The Task Force Report, the associated Press Release, and the Fact Sheet are also provided in the briefing materials for your information. In the task force report, recommendations were made regarding FDA's future direction for regulating nanomaterial-containing products. Guidance development was included as one the recommendations. With respect to CDER's position on this matter, while it is decided that specific guidances ought to be developed, for the short term, there are reasons why "nano-specific" requirements are not necessary. One reason is that the preclinical studies currently required of sponsors are very comprehensive, and include many studies that measure endpoints that could predict injury in many organ systems. Another reason is that, while some have suggested that the current preclinical screening tests might need to be tailored for the unique features of nanomaterial-containing products, no one has clearly communicated in what respect the current requirements might be lacking in their capacity to assess safety concerns from such products, and what might be other tests that would improve the predictive value of the current regulatory preclinical requirements. Nevertheless, because it is widely accepted that there are unique features associated with nanotherapeutic products, these unique features may lead to future challenges for the development, manufacturing, and possibly safety evaluation and review of these products. Consequently, it is felt that there may be room to consider developing guidance documents, focusing perhaps first on CMC (chemistry, manufacturing and controls) issues, since characterization is likely to be a challenge for

both the sponsor of nanotechnology-based products, as well as for regulatory agencies, who must regulate these products.

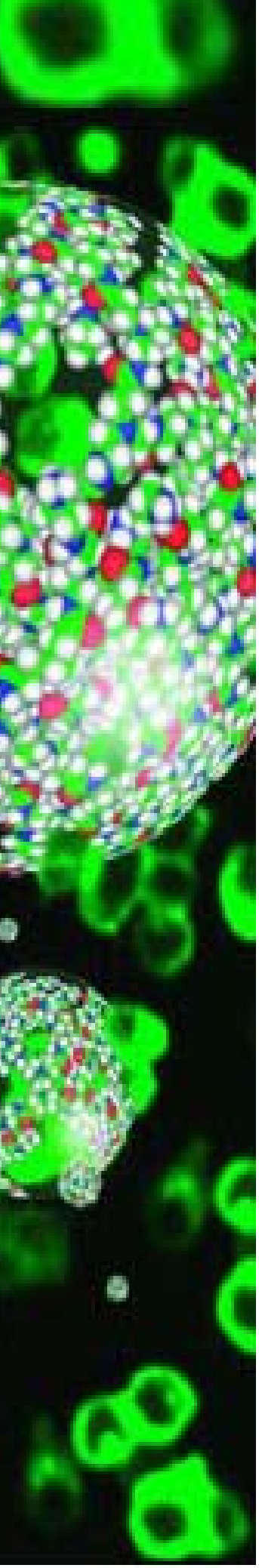
At this Advisory Committee meeting of the Office of Pharmaceutical Science, the session on nanotechnology will include presentations from academic and industry scientists working on the development of drug applications of nanotechnology.

Following the presentations, there will be a panel discussion where the committee will be asked the following questions:

1. Is CDER guidance needed for the development of nanotechnology derived drug applications?
2. If guidance is needed from CDER, what areas should these guidances focus on?
3. In light of the many definitions of nanotechnology available, how should CDER define nanotechnology, for the purposes of guidance development?

Other issues that have come up which you might wish to think about prior to the meeting:

- Are current CDER preclinical requirements adequate for the evaluation of nanomaterial-containing drugs?
- Should particle size information be routinely requested of drug developers, regardless of whether nanomaterials are included in the product? How might this information help in the assessment of safety and efficacy of drugs?
- Is CDER and OPS going in the right direction?
- What else should we be doing?



Nanotechnology

A Report of the

U.S. Food and Drug Administration

Nanotechnology Task Force

July 25, 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: July 23, 2007

TO: Deputy Commissioner for Policy
Associate Commissioner for Science

FROM: Commissioner of Food and Drugs

SUBJECT: Nanotechnology Task Force Report

Thank you for submitting to me the Nanotechnology Task Force Report. Nanotechnology holds great promise for the development of new treatments and diagnostics. However, as with other emerging technologies, it poses questions regarding the adequacy and application of our regulatory authorities. I commend you and the rest of the Nanotechnology Task Force on your efforts in developing this report and its recommendations to improve the FDA's scientific knowledge of nanotechnology and to address the regulatory challenges that may be presented by products that use nanotechnology. I appreciate the fact-finding efforts that the Task Force undertook, such as holding the October 2006 public meeting and soliciting public comment, to understand the issues and provide me with informed recommendations.

I endorse the report and its recommendations. This includes the recommendations to issue additional guidance to provide greater predictability of the pathways to market and for ensuring the protection of public health. Please move forward with these recommendations, pursuant to FDA's good guidance practice (GGP) process (21 CFR 0.115), as appropriate.

Andrew C. von Eschenbach, M.D.

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Executive Summary

As other emerging technologies have in the past, nanotechnology poses questions regarding the adequacy and application of regulatory authorities. The then Acting Commissioner of the Food and Drug Administration (FDA) initiated the Nanotechnology Task Force (Task Force) in 2006 to help assess these questions with respect to FDA's regulatory authorities, in light of the current state of the science for nanotechnology. This report offers the Task Force's initial findings and recommendations to the Commissioner.

The report includes:

- A synopsis of the state of the science for biological interactions of nanoscale materials;
- Analysis and recommendations for science issues; and
- Analysis and recommendations for regulatory policy issues.

The report addresses scientific issues as distinct from regulatory policy issues in recognition of the important role of the science in developing regulatory policies in this area, rapid growth of the field of nanotechnology, and the evolving state of scientific knowledge relating to this field. Rapid developments in the field mean that attention to the emerging science is needed to enable the agency to predict and prepare for the types of products FDA may see in the near future.

A general finding of the report is that nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies. However, these challenges may be magnified both because nanotechnology can be used in, or to make, any FDA-regulated product, and because, at this scale, properties of a material relevant to the safety and (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range. In addition, the emerging and uncertain nature of the science and potential for rapid development of applications for FDA-regulated products highlights the need for timely development of a transparent, consistent, and predictable regulatory pathway.

The Task Force's initial recommendations relating to scientific issues focus on improving scientific knowledge of nanotechnology to help ensure the agency's regulatory effectiveness, particularly with regard to products not subject to premarket authorization requirements. The report also addresses the need to evaluate whether the tools available to describe and evaluate nanoscale materials are sufficient, and the development of additional tools where necessary.

The Task Force also assessed the agency's regulatory authorities to meet any unique challenges that may be presented by FDA-regulated products containing nanoscale materials. This assessment focused on such broad questions as whether FDA can identify products containing nanoscale materials, the scope of FDA's authorities to evaluate the safety and effectiveness of such products, whether FDA should require or permit products to be labeled as containing nanoscale materials, and whether the use of nanoscale materials in FDA-regulated products raises any issues under the National Environmental Policy Act.

The Task Force concluded that the agency's authorities are generally comprehensive for products subject to premarket authorization requirements, such as drugs, biological products, devices, and food and color additives, and that these authorities give FDA the ability to obtain detailed scientific information needed to review the safety and, as appropriate, effectiveness of products. For products not subject to premarket authorization requirements, such as dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS), manufacturers are generally not required to submit data to FDA prior to marketing, and the agency's oversight capacity is less comprehensive.

The Task Force has made various recommendations to address regulatory challenges that may be presented by products that use nanotechnology, especially regarding products not subject to premarket authorization requirements, taking into account the evolving state of the science in this area. A number of recommendations deal with requesting data and other information about effects of nanoscale materials on safety and, as appropriate, effectiveness of products. Other recommendations suggest that FDA provide guidance to manufacturers about when the use of nanoscale ingredients may require submission of additional data, change the product's regulatory status or pathway, or merit taking additional or special steps to address potential safety or product quality issues. The Task Force also recommends seeking public input on the adequacy of FDA's policies and procedures for products that combine drugs, biological products, and/or devices containing nanoscale materials to serve multiple uses, such as both a diagnostic and a therapeutic intended use. The Task Force also recommends encouraging manufacturers to communicate with the agency early in the development process for products using nanoscale materials, particularly with regard to such highly integrated combination products.

The guidances the Task Force is recommending would give affected manufacturers and other interested parties timely information about FDA's expectations, so as to foster predictability in the agency's regulatory processes, thereby enabling innovation and enhancing transparency, while protecting the public health.

Introduction

Nanoscale materials often have chemical, physical, or biological properties that are different from those of their larger counterparts. Such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity. Because of these properties, nanoscale materials have great potential for use in a vast array of products. Of particular interest to the Food and Drug Administration (FDA, the agency), nanoscale materials may enable new developments in products to advance public health. Also because of some of their special properties, nanoscale materials may pose different safety issues than their larger or smaller (i.e., molecular) counterparts.

FDA is generally responsible for overseeing the safety and effectiveness of drugs and devices for humans and animals, and of biological products for humans. The agency is also generally responsible for overseeing the safety of foods (including food additives and dietary supplements), color additives, and cosmetics.[1] The agency conducts these oversight functions under a variety of laws and regulations, which establish the specific pre-market and/or post-market oversight mechanisms applicable to a particular class of products. Most of the laws and regulations under which FDA operates were written before the advent of nanotechnology. Most are general in nature by design, however, offering flexibility to accommodate products made with new technologies or containing new kinds of materials.

Research and development relating to nanotechnology applications promises the development of products having multiple, highly integrated functions. FDA will need to anticipate this shift in the nature of products received for review and authorization. For example, disease diagnosis, drug targeting, and non-invasive imaging elements are being combined in individual nanotechnology products.[2] A goal of this report is to assist in the development of a transparent, consistent, and predictable regulatory pathway for such products.

More broadly, this report is intended to outline ways in which FDA can both (1) enhance its knowledge of nanotechnology to support its oversight for products using such technology and (2) inform interested stakeholders of what information may need to be developed to support the marketing of FDA-regulated products that use nanoscale materials.

FDA is a member agency in the National Nanotechnology Initiative (NNI), a federal research and development program established to coordinate the multi-agency efforts in

[1] Among other requirements, the Federal Food, Drug, and Cosmetic Act requires that drugs and devices be safe, and the Public Health Service Act requires that biological products be safe. Among other requirements, the FFDCA states that food and cosmetics must not be adulterated. For convenience, in this report the term "safe" is used not only in reference to drugs, devices, and biological products but also in reference to foods and cosmetics as an approximate short-hand for "not adulterated." See 21 USC 342, 361, defining the term "adulterated" for foods and cosmetics. In addition to regulating their safety, the agency also regulates use claims made with regard to foods and cosmetics, including claims regarding the effects of these products. However, in keeping with the primary focus of the Task Force's mandate, this report addresses mainly issues relating to the safety of these products.

[2] See for example descriptions of research and development activities at: http://nint-innt.nrc-cnrc.gc.ca/research/index_e.html; http://www.jst.go.jp/kisoken/nano/en/VirlaboResearchY01.html ; http://nano.cancer.gov/resource_center/cancer_nanotechnology_brochure.pdf.

nanoscale science, engineering, and technology. The goals of the NNI are to: (1) maintain a world-class research and development program aimed at realizing the full potential of nanotechnology; (2) facilitate transfer of new technologies into products for economic growth, jobs, and other public benefit; (3) develop educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and, (4) support responsible development of nanotechnology. FDA centers are conducting nanoscale material research within programs that support their specific regulatory priorities. Participation in the NNI provides FDA and the other regulatory and research funding agencies the opportunity to define their research needs.

Task Force Mission

In August 2006, then Acting Commissioner of Food and Drugs, Andrew C. von Eschenbach, M.D., announced the formation of an internal FDA Nanotechnology Task Force. He charged the Task Force with determining regulatory approaches that would enable the continued development of innovative, safe, and effective FDA-regulated products that use nanoscale materials.[3] The Task Force was asked to identify and recommend ways to address any knowledge or policy gaps that exist to better enable the agency to evaluate safety aspects of FDA-regulated products that contain nanoscale materials. Specifically, the Task Force was directed to:

- Chair a public meeting to help FDA further its understanding of developments in nanoscale materials that pertain to FDA-regulated products, including new and emerging scientific issues such as those pertaining to biological interactions that may lead to either beneficial or adverse health effects;

- Assess the current state of scientific knowledge pertaining to nanoscale materials for purposes of carrying out FDA's mission;

- Evaluate the effectiveness of the agency's regulatory approaches and authorities to meet any unique challenge that may be presented by the use of nanoscale materials in FDA-regulated products;

- Explore opportunities to enable innovation using nanoscale materials to develop safe and effective drugs, biologics and devices, and to develop safe foods, feeds, and cosmetics;

- Continue to strengthen FDA's collaborative relationships with other federal agencies, including the agencies participating in the NNI such as the National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA), as well as with foreign government regulatory bodies, international organizations, healthcare professionals, industry, consumers, and other stakeholders, to gather information regarding nanoscale materials used or that could be used in FDA-regulated products;

- Consider appropriate vehicles for communicating with the public about the use of

[3] For additional information on the Task Force, including its membership, see http://www.fda.gov/nanotechnology/nano_tf.html.

nanoscale materials in FDA-regulated products; and

- Submit its initial findings and recommendations to the Commissioner within nine months of the public meeting.

As requested by the Commissioner, the Task Force opened a public docket and held a public meeting on October 10, 2006. The objectives of the meeting and the docket were to learn about:

- New nanoscale material products under development in the areas of foods (including food additives and dietary supplements), color additives, animal feeds, cosmetics, drugs and biologics, and medical devices;

- New or emerging scientific issues that should be brought to FDA's attention, including issues related to the safety of nanoscale materials; and

- Any other issues concerning the use of nanoscale materials in FDA-regulated products regarding which regulated industry, academia and the interested public wished to inform FDA.

Following the public meeting, the Task Force:

- Reviewed both the oral and written comments it received;

- Assessed the current state of nanotechnology-related science; and

- Evaluated the scope of the agency's current authorities to meet any unique challenges presented by the use of nanoscale materials in FDA-regulated products.

Definitions for Nanotechnology and Related Terms

Nanotechnology allows scientists to work on the scale of molecules to create, explore, and manipulate the biological and material worlds measured in nanometers, one-billionth of a meter. By way of comparison, a sheet of paper is about 100,000 nanometers thick; a human hair is about 80,000 nanometers wide.

FDA regulates a wide range of products, which may use a wide range of materials for varied purposes inside and outside the body. The Task Force has sought to apply a sufficiently comprehensive analytical approach to address the scientific and policy issues FDA must consider to protect and promote human and animal health in regulating products within its jurisdiction that use nanoscale materials. Accordingly, the Task Force has considered a broad array of available information on a wide range of products, materials, techniques, and technologies. The Task Force has not adopted a precise definition for "nanoscale materials," "nanotechnology," or related terms to define the scope of its work. The Task Force concluded that it would be most productive to take a broadly inclusive approach in identifying potentially relevant studies, data, and other information.

The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, while one definition for "nanotechnology," "nanoscale material," or a related term

or concept may offer meaningful guidance in one context, that definition may be too narrow or broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products.[4]

Organization of this Report

This report provides the Task Force's initial findings and recommendations. The report is divided into three sections. The first section discusses scientific knowledge of the potential effects of nanoscale materials relevant to FDA's regulation of products. The second section assesses scientific issues relating to FDA's regulation of products using nanoscale materials. The third section assesses the agency's regulatory authorities as these authorities relate to FDA-regulated products using nanoscale materials. The report takes into account comments submitted to relevant public dockets and made at the public meeting, and then presents recommendations to the Commissioner for actions the agency can take in furtherance of its mission to protect and promote the public health.

[4] The Task Force notes that the use of the terms "nanoscale materials," "nanoscale particles", and "nanotechnology" in this report does not reflect a Task Force position as to how these or related terms should be used or defined for regulatory purposes, including for purposes of any information requests or guidance recommended in this report.

State of the Science of Nanotechnology Relevant to FDA

The science and applications of nanotechnology are developing at a very rapid pace. In 1990, approximately 1,000 scientific publications on nanotechnology were published and approximately 200 patent applications (worldwide) were filed.[5] By 2002, the number of publications had risen to over 22,000 with over 1,900 patent applications. This exponential increase in scientific publications and patents is the result of increased discovery and investment in nanotechnology that will likely result in substantial and continual changes in products falling under the regulatory authority of the FDA.

Numerous reviews have been published focusing on the state of knowledge of behavior, interaction with biological systems (both for advantageous and toxicity outcomes), and potential environmental disposition of nanoscale materials. Government bodies have published some of these,[6] as have private entities focusing on the risk associated with nanoscale materials,[7] and still others can be found in the peer-reviewed public literature.[8] Often these reports stress the need for research on: characterization of materials in the nanoscale range; methods for identifying hazards; understanding biological response to nanoscale materials; and characterizing nanoscale material exposure and transport (in humans and the environment).

Identifying precisely what qualifies as a nanoscale material is difficult and currently a subject of substantial discussion in the scientific, regulatory, and standards communities. As a result, developing a comprehensive description of products that are currently produced with nanotechnology, or may be produced with this technology in the future, would be difficult at best, and likely infeasible. Instead this report considers examples based on what is currently known about use of this technology.

Perhaps of greatest relevance to products regulated by FDA is what the current study of structures in the nanoscale range is teaching about biological interactions.

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[5] Heinze, T. 2004. Nanoscience and nanotechnology in Europe: Analysis of publications and patent applications including comparisons with the United States. *Nanotechnology Law & Business* **1**(4): 10.

[6] Australian Safety and Compensation Council. A Review of the Potential Occupational Health & Safety Implications of Nanotechnology. July 2006. ISBN 0 642 32609 6; Borm,P.J.A.,et al. 2006. The potential risks of nanomaterials: a review carried out for ECETOC. *Particle and Fiber Toxicology* **3:** 11. National Nanotechnology Initiative (NNI). 2006. Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. Available at www.nano.gov.

[7] Davies, J.C. 2006. Managing the effects of Nanotechnology. Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano; ICF International. 2006. Characterizing the environmental, health, and safety implications of nanotechnology: Where should the federal government go from here? ICF international, Fairfax, VA. Available at www.icfi.com; Maynard, A.D. 2006. Davies, J.C. 2006. Nanotechnology: A research strategy for addressing risk. Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano; Taylor, M.R. 2006. Regulating the products of nanotechnology: Does the FDA have the tools it needs? Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano .

[8] Chan, V.S.W. 2006. Nanomedicine: An Unresolved Regulatory Issue. *Regulatory Toxicology and Pharmacology*, **46** (3): 218-224; Davis, J.M. 2007. How to assess the risks of nanotechnology: Learning from past experience. *J. Nanoscience and Nanotechnology*, **7** 1-8.; Oberdörster, G., et al. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ. Health Perspect*. **113**: 823-829.

In light of the current state of the science, an understanding of the interactions of nanoscale materials with biological systems is probably best gained through case-by-case analysis of specific types of nanoscale materials and of variations in their characteristics. However, recent reviews have developed initial approaches for more general description of the kinds of interactions that might be expected with biological systems.[9] Generalized approaches to organizing information for risk assessment and risk management of nanoscale materials have also been developed that provide insight for how biological interactions of nanoscale materials might be understood.[10]

Generalizable Knowledge of Biological Interactions

Generalizable principles are being derived from studies of specific types of nanoscale materials. For instance, studies in some laboratories have determined that surface area per unit of volume or mass can be a better measure than mass for assessing relative toxicity across particle size and material variations.[11] This tells us, for example, that the suitability of mass-based dose measurements should be evaluated before drawing conclusions about potency of a drug effect or about toxic response. However, it is important to recognize that in some cases surface area has been shown to be a much less important determinant of biological interaction than surface modification (for example, binding different chemical groups to the surface of a particle) for those particular types of particles in which this has been examined systematically.[12] This indicates that one should pay particular attention to the composition and surface characteristics of nanoscale materials that may come in contact with biological systems.

In some cases, features of materials such as charge or the position of the surface modification have been found to affect toxicity.[13] For example, positively charged nanoscale lipid vesicles (nanovesicles) induced cerebral edema, but neutral nanovesicles and

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[9] Tsuji JS et al. Research strategies for safety evaluation of nanomaterials, part IV: risk assessment of nanoparticles. *Toxicol Sci* 2006 **89**(1): 42-50; Oberdörster, G., et al., Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. *Part Fibre Toxicol* **2**: 8 2005.
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf
http://www.nanotec.org.uk/finalReport.htm

[10] Morgan, K. Development of a Preliminary Framework for Informing the Risk Analysis and Risk Management of Nanoparticles. *Risk Analysis*, **25**(6): 1621-1635 2005.

[11] Warheit DB, et al. Pulmonary Bioassay Studies with Nanoscale and Fine-Quartz Particles in Rats: Toxicity is Not Dependent upon Particle Size but on Surface Characteristics. Toxicological Sciences 2007 95(1):270-280.; Warheit DB, et al. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations: Impact of surface treatments on particle toxicity. *Toxicological Sciences* **88**(2): 514-524 2005.

[12] Hoshino A, et al. Physicochemical properties and cellular toxicity of nanocrystal quantum dots depend on their surface modification. *Nano Letters* **4**(11): 2163-2169 NOV 2004; Warheit DB, et al. Pulmonary Bioassay Studies with Nanoscale and Fine-Quartz Particles in Rats: Toxicity is Not Dependent upon Particle Size but on Surface Characteristics. *Toxicological Sciences* 2007 **95**(1):270-280.; Warheit DB, et al. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations: Impact of surface treatments on particle toxicity. *Toxicological Sciences* **88** (2): 514-524 2005.

[13] It is important to note with respect to the development of general knowledge that many of the studies published in the literature have been conducted with nanoscale materials that are either poorly characterized, or not characterized. Therefore, in many cases the quality and applicability of the findings reported may be inadequate.

low concentrations of negatively charged nanovesicles did not.[14] Studies have also shown that modifying the surface of nanoscale materials with surfactants or biocompatible polymers (e.g., polyethylene glycol, PEG) reduced the toxicity *in vitro*[15] and altered the half-life and tissue deposition *in vivo*.[16] Such findings are relevant to drug delivery for example, for understanding the potential distribution of nanoscale materials in the body, and for evaluating toxicity and biocompatibility. However, these findings are material-specific and, we are not aware of methods or models that would extend these findings to provide a better understanding of broad classes of materials.

There is also well-developed literature on biological interactions of naturally occurring particles or particles released from industrial processes that include particles in the nanoscale range, such as combustion-related particulate matter, silica dust, and biological particles. These data sets may provide valuable information for understanding generalizable properties of nanoscale particles. However, because of the great significance of surface modification to the properties of nanoscale particles that has been shown in some cases, the value of these existing data that deal with widely variable nanoscale particle subtypes may be limited to understanding of basic issues such as biological filtering and dose metrics.

Predictability of Biological Interactions

At a first level of approximation, understanding simple particle movement into or from one compartment to another in the body involves consideration of various absorption and transport mechanisms that either passively keep particles from entering some areas of the body depending on how large they are, or actively move the particles. An understanding of these mechanisms can help predict what movement might occur for particular nanoscale particles. Accordingly, the significance of size to biological interaction may be relatively straightforward to predict and assess in many cases where changing particle size can be expected to affect absorption and transport mechanisms.

Furthermore, if a specific kind of surface reactivity is known for a material, then it might be expected that the reactivity per unit of mass would increase with decreasing particle size because specific surface area would increase. It could also, therefore, be predicted that important biological effects could arise when the surface area is substantially increased with the same mass of exposure. The argument has been made, for example, that generation of reactive oxygen species for some particles may increase as particle size decreases and surface area increases, leading to increased inflammatory response in lung tissue.[17] The particle size range or particle concentrations at which such an increase in reactivity could cause adverse effects would depend on adaptive responses of the affected biologic system, however, and, therefore, would be difficult to predict in the absence of test data.

In addition, biological interaction may be focused such that only a specific particle size range will have biological effects. For example, there may be an upper size limit for dermal

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[14] Lockman PR, et al. Nanoparticle surface charges alter blood-brain barrier integrity and permeability, *J. Drug Target.* **12**(9-10): 635-641 (2004).
[15] Derfus AM, et al. Probing the cytotoxicity of semiconductor quantum dots, *Nano Lett.* **4**(1):11-18 (2004).
[16] Ballou B, et al. Noninvasive imaging of quantum dots in mice, *Bioconjugate Chem.* **15**(1): 79-86 (2004).
[17] Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. *Toxicol Appl Pharmacol* 2001, **175**:191-199.

absorption of any specific type of particle, though that limit may vary based on other factors as well (e.g., particle charge or chemical properties, conditions of dermal exposure). A compound that previously was excluded from exposure to internal tissues might then produce effects, beneficial or adverse, due to the exposure of internal tissues when particle size decreased below the threshold for exclusion. These effects could be based on somewhat simple physical interaction, such as the filtering capacity of phagocytic cells, transport effects of capillary structures, or adhesion to proteins or other molecules in biological fluids.[18] In some cases, these interactions may be predictable, for example, based on knowledge of the size of materials that can pass through capillary walls. In others, data could be developed that would allow better prediction of biological interaction, for example regarding size-dependent dermal absorption as is being developed by FDA in collaboration with the National Toxicology Program.[19]

Biological interactions influenced by the particular chemistry and physical configuration of the nanoscale material might also occur in ways that are unpredictable without specific test data for the material. For example, similar to how charge and functional group locations on a molecule will affect interactions with chemicals in the body, characteristics such as a particle's shape and the location of changes in its surface may affect the interactions of nanoscale materials with chemicals in the body.

The available information does not suggest that all materials with nanoscale dimensions will be hazardous. Furthermore, if all nanoscale materials are compared to all non-nanoscale materials, whether larger or smaller, it is not apparent that the nanoscale materials as a group would have more inherent hazard. However, consideration of the basic science of how materials interact with biological systems does indicate that a material's properties can change when size is increased or decreased into, or varied within, the nanoscale range.

Science Issues

Introduction

Virtually any product category regulated by FDA might currently or in the future involve uses of nanotechnology somewhere in the manufacturing process. A somewhat smaller set of products can be expected to retain nanoscale structures in the finished product, such as systemically bioavailable nanoscale drugs or nanoscale particles or nanoscale structures in solid objects that may release nanoscale materials through use. As discussed above, the biological interactions of regulated products using nanoscale materials are of particular importance to FDA. This section addresses scientific issues relevant to FDA. They relate to:

- Understanding of interactions of nanoscale materials with biological systems; and

[18] Lynch I. 2007. Are there generic mechanisms governing interactions between nanoparticles and cells? Epitope mapping the outer layer of the proteinBmaterial interface. *Physica A: Statistical and Theoretical Physics* **373**: 511-520.
[19] Description of the NTP's Nanotechnology Safety Initiative at**:** http://ntp.niehs.nih.gov/go/20837.

- Adequacy of testing approaches for assessing safety, effectiveness, and quality of products containing nanoscale materials.

We will address both issues below, taking into account relevant comments submitted to the public docket for the FDA Nanotechnology Task Force's October 2006 public meeting and to the docket opened in response to a petition submitted by the International Center for Technology Assessment (ICTA) and other parties entitled, Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (ICTA Petition).[20] In addition to other resources, the Task Force also considered the US Government-wide evaluation of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials (NNI 2006c)[21] in developing this discussion and these recommendations.

Issue: Understanding Interactions of Nanoscale Materials with Biological Systems

Comments

Many comments noted that nanoscale materials can have a wide variety of properties that are markedly different from the same materials in larger scale forms. Some comments suggested that the definition of "nanomaterial" should be limited to those materials that have some unique, qualitatively different, properties derived from their physical scale. Some comments noted that although the nature and unique properties of many nanoscale materials are not well understood, some nanoscale materials have been observed to be toxic in certain assays and under some specified conditions, or, based on their behavior in biological systems, raise suspicions of potential toxicity. .

Some comments stated that nanoscale materials have a unique ability to interact with proteins and other essential biological functional elements. Some noted: that nanoscale materials can be more biologically active than non-nanoscale materials; that basic research is needed on such issues as interactions with subcellular structures and dose/concentration; and that such research should take an interdisciplinary approach, making use of experts in toxicology, materials science, medicine, molecular biology and bioinformatics. The comments pointed out that there are differences in dose-response curves depending on whether the curves are expressed by mass, number of particles, or surface area.

Some comments essentially stated that, because properties or safety of nanoscale materials cannot be assumed or inferred from larger-scale forms, nanoscale materials will need to be directly and adequately evaluated. Some comments highlighted that this lack of proven safety may be a particularly significant concern for ingested products.

Other comments noted that there is a great deal of knowledge about behavior of many types

[20] FDA is currently reviewing this petition. FDA has not yet reached a decision on the petition because it raises complex issues requiring extensive review and analysis by agency officials, and in relation to which the agency is seeking public input. While this report addresses some issues raised in the petition, this report reflects only the views of the Task Force, and does not constitute an agency answer to the petition in whole or in part.

[21] National Nanotechnology Initiative (NNI). 2006. Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. Available at www.nano.gov.

of nanoscale materials, that there are established methods for assessing their safety and effectiveness, and that the novelty of the scientific issues posed by nanoscale materials is exaggerated. One comment stated that the nanoscale materials contained in some newer sunscreens have been well tested by industry already and have had their safety established. Some comments noted that the use of nanoscale materials may enable development of more targeted drugs and biological products, which may be safer and more effective than otherwise possible, and development should not be impeded.

Some comments highlighted the need for FDA to have adequately trained and educated staff to review products that may contain nanoscale materials.

Analysis

Issues Relevant to all Regulated Products

There may be a fundamental difference in the kind of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way that testing is performed. For conventional chemicals, there is a relatively long history of exploring, and a correspondingly relatively robust understanding, of interactions of molecular classes (such as compounds with particular structures or functional groups) with biological systems. In some cases, screening test methods are used to define what additional tests may need to be performed to gain sufficient knowledge about safety and/or effectiveness. For example, there are screening tests available to help identify whether DNA damage is a possible outcome from exposure to a certain chemical. Other tests can tell how the chemical is distributed in the body and in what forms it is present in various tissues. FDA has an expectation relevant to molecular forms of materials used in products that FDA regulates that if the molecule does not cause DNA damage during *in vitro* testing, or if it is metabolized quickly and does not reach sensitive organs, or if it is not absorbed, then it is less likely to present certain kinds of health hazards. This expectation is based on long experience with, and consequent understanding of, basic biological interactions of molecular forms of chemicals and of how these interactions correlate with the results of current testing methods.

The testing methods for different product types also may need to be evaluated to determine whether or how they can be used in assessing the bioavailability of nanoscale materials in humans. This issue is not so much one of whether the tests are valid (as discussed under "Adequacy of testing approaches…" below). Rather, it speaks to the familiarity with the predictive value of the tests. There is, comparatively speaking, more familiarity with the predictive value of such tests for molecules than for nanoscale materials. As FDA and the scientific community develop familiarity with different nanoscale material types, it may be possible to predict, for example, that specific variations in characteristics of a type of nanoscale material may cause it to be reactive in the same way that it is known that addition of a chemical-specific functional group may cause a molecule to be reactive.

Several recent scientific reviews conclude that the state of knowledge for biological interactions of nanoscale materials is generally in need of improvement to enhance risk assessments and better support risk management decisions.[22] For example, the information

[22] http://www.nano.gov/NNI_EHS_research_needs.pdf; http://www.nanotec.org.uk/finalReport.htm

available on biological interactions for nanoscale materials primarily applies to the specific materials tested, and the agency is not aware of models for how the information might be applied more broadly to other nanoscale materials. At this stage, it is important to monitor individual hazard studies of specific nanoscale materials and, where possible, seek to synthesize a common understanding of more general material properties from these studies.

There is a potential to develop and organize information using physiologically based pharmacokinetic (PbPk) models or quantitative structure activity relationship (QSAR) models, to enable formulation of generalized principles for the behavior of classes of nanoscale materials. Integration of information with respect to given material characteristics (for example, material type, size, charge, surface modification) could be of particular benefit in improving general understanding. Such models are useful in predicting biological interactions of molecules and may provide the same sort of value for nanoscale materials. At present, however, the agency is not aware of models such as these for nanoscale materials.

Further, even though there is a broad array of ongoing research across a wide variety of disciplines, the different disciplines and laboratories employ different methods, standards and ontologies. As mentioned previously, in 2002 alone there were 22,000 scientific publications relating to nanotechnology.[23] Managing this information is a formidable task, but data mining would likely yield a wealth of information relevant to the FDA's review of nanotechnology-based products. For these reasons, the development of a comprehensive database employing standardized ontologies, or other means of integration, could be very valuable.

Rendering appropriate regulatory decisions requires up-to-date training and information. FDA's ability to accomplish its mission depends in part on having staff with expertise in areas such as pharmacology, materials science, biology, physics, chemistry, medicine, and toxicology. New and emerging nanotechnology-based products highlight the possible need for new expertise for some review areas. For example, characterization methods for nanoscale materials (e.g., describing size, shape, surface topography) generally require use of different equipment than would be used for characterizing molecules. The data produced by this equipment are different than those generated by chemical analysis methods typically seen by most FDA reviewers. Particularly in light of the evolving nature of scientific knowledge and technical capacity relating to nanotechnology, it will be important to ensure ongoing training, as well as dissemination of new information within review centers and more broadly across the agency, to ensure timely, informed consideration of the most current science.

Products Subject to Premarket Authorization

As discussed more fully below in the Regulatory Policy Issues section, for products subject to premarket authorization, such as drugs, devices, biologics, and food and color additives, FDA reviewers can require manufacturers to provide the necessary scientific information to support regulatory decisions. The evolving scientific understanding of nanoscale materials would generally be expected to inform assessment of what data are needed. For example,one currently would expect the information needed to assess biological interaction to change as

[23] Heinze, T. 2004. Nanoscience and nanotechnology in Europe: Analysis of publications and patent applications including comparisons with the United States. *Nanotechnology Law & Business* **1**(4): 10.

size decreases because, as discussed above, data from larger particles may not necessarily predict behavior for smaller particles. However, a precise size boundary where scientific information based on larger particles becomes less relevant for a particular question or material is not currently apparent. Similarly, research identifying short and long-term toxicity issues relevant to particular nanoscale materials could aid FDA in determining what, if any, additional testing a manufacturer should conduct. In short, a greater understanding of the properties of nanoscale materials and of trends in material development and uses would help focus data and testing requirements.

Products Not Subject to Premarket Authorization

For products not subject to premarket authorization by FDA, such as cosmetics and dietary supplements, the agency generally does not receive data, including safety data, before the products are marketed. Furthermore, there are no post-marketing reporting requirements for adverse events associated with cosmetics. Therefore, FDA receives only cosmetic adverse event reports that are submitted voluntarily. Similarly, for dietary supplements, to date FDA has received only voluntarily submitted adverse events, although recently enacted legislation will give FDA greater access to dietary supplement adverse event reports in the future.[24]

The agency may have far less baseline data than with products subject to premarket authorization. As a result, the agency may have a comparatively difficult burden in assembling the necessary data to support a product removal action under these authorities (whether the product contains nanosized or other materials).

Also as discussed above, there may be general differences in properties relevant to evaluation of safety and effectiveness (as applicable) of products using nanoscale materials compared to products using other materials. For example, size, shape, and charge of a nanoscale material can affect disposition or toxicity in the body in ways that differ from molecular forms of materials and that may be generalizable across different particle or other material types. Knowledge of such generalized differences could, for example, help inform FDA's: assessments of whether to take regulatory actions against products not subject to premarket authorization; efforts to obtain and develop further information; and efforts to develop guidance on data needs for products not subject to premarket authorization.

Recommendations for Consideration

The Task Force recommends strengthening FDA's promotion of, and participation in, research and other efforts to increase scientific understanding, to facilitate assessment of data needs for regulated products. Such activities should, where appropriate, be coordinated with and leveraged against activities supported by other Federal agencies, the private sector, or other countries. This would include:

- Promoting efforts, and participating in collaborative efforts, to further understanding of biological interactions of nanoscale materials, including, as appropriate the development of data to assess likelihood of long term health effects from exposure to

[24] Beginning December 22, 2007, any serious adverse events associated with a dietary supplement reported to the product's manufacturer, packer, or distributor will have to be submitted to FDA. In addition, firms will have to keep records of all dietary supplement adverse events, serious or non-serious, and FDA will have access to those records during inspections.

specific nanoscale materials;

- Assessing data on general particle interactions with biological systems and on specific particles of concern to FDA;
- Promoting and participating in collaborative efforts, to further understanding of the science of novel properties that might contribute to toxicity, such as surface area or surface charge;
- Promoting and participating in collaborative efforts to further understanding of measurement and detection methods for nanoscale materials;
- Collecting/collating/interpreting scientific information, including use of data calls for specific product review categories (see Regulatory Policy Issues section);
- Building in-house expertise;
- Building infrastructure to share and leverage knowledge internally and externally, seeking to collect, synthesize, and build upon information from individual studies of nanoscale materials; and
- Ensuring consistent transfer and application of relevant knowledge through establishment of an agency-wide regulatory science coordination function for products containing nanoscale materials.

Issue: Adequacy of Testing Approaches for Assessing Safety and Quality of Products Containing Nanoscale Materials

Comments

Several comments expressed the concern that existing toxicology screening methods will not adequately assess toxicologic properties of nanoscale materials, and that these methods cannot be used in their present form to assess engineered nanoscale materials. Some comments pointed out that pharmacokinetics and pharmacodynamics of nanoscale particles are different from those of larger particles and that existing toxicity screening studies do not take these differences into account. Several comments further recommended that cellular assays should reflect exposure media (e.g., air, water, food), route of exposure, and portal-of-entry toxicity (e.g., toxicity to lungs, skin, mucus membranes), as well as systemic responses.

Comments stated that most toxicology tests are short-term, and might leave long-term effects unevaluated, especially because the long-term toxicity and effects for most nanoscale materials remain unknown. These comments noted that appropriate endpoints for *in vitro* assays can be difficult to determine, as single cell types are often not sufficient for evaluation of the function or health of organs or tissues that are made up of multiple cell types, and given that various types of tissues are exposed in the body.

Other comments were directed to the inadequacy or absence of currently available and

standardized product characterization methodologies for nanoscale materials. A comment highlighted that FDA has limited ability to detect nanoscale material components in some products. Another comment emphasized that FDA's ability to inspect products is also presently significantly limited with regard to products that may contain nanoscale materials. One comment recommended that nanoscale material be characterized with respect to size (surface area and size distribution), chemical composition (such as purity and crystallinity), surface structure (surface reactivity, surface groups, inorganic/organic coatings, etc.), solubility, shape and aggregation. Other comments noted that detection of nanoscale materials requires expensive and sophisticated equipment, and it is often unclear which parameters are relevant to toxicity.

Comments also encouraged FDA to work with other government agencies to develop rapid screening tools for these types of products. Several comments noted that the Nanotechnology Characterization Laboratory, run by the National Cancer Institute, will be very useful in helping to characterize nanoscale materials and to develop standards and standardized methods for measuring nanoscale materials.

Analysis

Assays to Develop Biological Effects Data

Established *in vitro* and *in vivo* assays and predictive models are available to evaluate a variety of endpoints relevant to the establishment of hazard(s) and the identification of further testing needs. The results of these tests are often used in a tiered approach in an overall data development process for understanding the toxicity and effectiveness of a product such that, for example, a “positive” response may lead to a conclusion of hazard or the initiation of additional studies and a “negative” response would not (the obverse may also be true). However, because many of these tests were developed for molecular forms of materials, and nanoscale materials may behave differently, the ability of these tests to support decisions about biological effects or further testing requirements need to be evaluated.

For example, data to support understanding of dose-response developed through *in vitro* test systems might not be appropriate for particles where sedimentation velocities and diffusion can change the delivered dose.[25] Similarly, in some cases it may be necessary to develop information to evaluate whether current short-term tests provide sufficient predictive value regarding the need for chronic or other long-term toxicity testing, and in some cases the only way to get this information may be to actually conduct long-term toxicity testing. In addition, development of new testing methods may be necessary to develop data to support decisions for nanoscale materials that may have novel biological responses.

Existing information for nanoscale materials does not appear to indicate a need for revision to all tests however. Accordingly, a tiered or staged approach to evaluation would seem appropriate. The first stage of such an approach would be to determine whether any specific tests may need evaluation. Subsequent stages would call for data to assess individual test methods as needed.

[25] Teeguarden,J.G., Hinderliter, P.M., Orr, G., Thrall, B.D., and Pounds, J.G. 2007. Particokinetics in vitro: Dosimetry considerations for in vitro nanoparticle toxicity assessments. *Toxicol. Sciences* **95**: 300-312.

Standard approaches for handling of materials for testing will also need to be evaluated and may need to be modified, with respect to such factors as appropriate solvents and dosing formulations, methods to prevent agglomeration of particles, stability conditions, and other variables that may affect test results when nanoscale materials are tested. Such adjustments may be needed to improve the reliability, repeatability, reproducibility and accuracy of assays and methods.

Metrology - Characterization of Particles in the Nanoscale Range

Currently, ability to detect nanoscale materials in the body or in products regulated by FDA is limited, and development of appropriate analytical methods for classes of products and of nanoscale materials may require substantial effort. Further, new analytical methods, and methods that FDA reviewers are generally less familiar with, are often used to characterize nanoscale materials. The strengths and limitations of these methods may vary in ways relevant to evaluating characteristics such as particle size, size distribution, surface charge, surface properties, and particle interactions (such as aggregation) that may be relevant to dose, stability, or other characteristics significant to biological interaction or product quality.

Inspection

Tests used for inspections and product surveillance will need to be evaluated to determine whether modifications are warranted to address nanoscale materials. Increased use of materials in the nanoscale range may present particular challenges, for example, relating to tests that assess product stability or development of potentially hazardous byproducts. Further, as with any product, scaling up to full production rates may affect such factors as purity, particle behavior, size distribution, and general batch-to-batch consistency, and it may be necessary to evaluate the adequacy of existing testing to assess such consequences of scale-up for products using nanotechnology.

Standardization of Tests and Data Reporting

In many cases, methods currently used to characterize nanoscale materials have not been standardized through recognized standard development organizations. There is a need to develop standard particle characterization methods. Furthermore, given the range of methods being used and being developed for nanoscale materials, there is a need to develop consistent nomenclature and measurement types and formats for use across studies and data submissions similar to the "MIAME" approach developed for microarray data.[26] Consistent reporting approaches will make data from one laboratory or for one material type more readily comparable to data from other laboratories and more useful to subsequent consideration of properties of the same type of material or other material types.

Recommendations for Consideration

To be marketed, FDA regulated products must be safe and, as applicable, effective. FDA-

[26] Minimum Information About a Microarray Experiment www.mged.org/Workgroups/MIAME/miame.html. Consistent reporting approaches can be established and instituted without adopting substantive definitions for "nanotechnology" and related terms for regulatory purposes (the merits of which may take some time to evaluate as explained above).

regulated products must also meet all applicable good manufacturing practice and quality requirements. Adequate testing methods are needed regardless of whether a product is subject to premarket authorization or not. Accordingly, the following recommendations are relevant to all categories of FDA-regulated products. The agency should:

- Evaluate the adequacy of current testing approaches to assess safety, effectiveness, and quality of products that use nanoscale materials;
- Promote and participate in the development of characterization methods and standards for nanoscale materials; and
- Promote and participate in the development of models for the behavior of nanoscale particles *in-vitro* and *in-vivo*.

The Task Force recommends encouraging manufacturers to consult with the agency regarding the appropriateness of testing methodologies for evaluating products using nanoscale materials.

Regulatory Policy Issues

Background

FDA regulates a broad range of products under the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Public Health Service Act (PHS Act). The agency's statutory authorities subject some types of products to premarket authorization requirements, either individually or by category, while permitting other products to be marketed without prior agency authorization.[27]

Products subject to premarket authorization include drugs, biological products, devices, and food and color additives. As detailed below, new drugs,[28] biological products, and devices receive marketing authorization on a product-by-product basis. FDA authorizes food additives and color additives for marketing by issuing a regulation approving a substance that meets prescribed identity and quality specifications for specified food additive or color additive uses under specified conditions. Once such a regulation is in place, it covers all products that comply with the regulation, and individual premarket review of such products

[27] For purposes of this report, the term "premarket authorization" is used to refer to a number of regulatory actions that the FFDCA and the PHS Act and agency regulations may refer to by other names, including "approval," "clearance," "licensing," and "listing." As used in this report, "premarket authorization" includes both premarket approval for an individual product (e.g., under an NDA, BLA, or PMA) and regulations permitting the marketing or use of an ingredient or substance for specified uses under specified conditions (e.g., a food additive regulation, OTC drug monograph, or color additive listing regulation). Among other issues concerning the use of nanotechnology, this report focuses on how to treat nano versions of existing products that fall under such a regulation and makes recommendations to guide agency consideration of that issue.

[28] Generally, a drug is regulated as a "new" drug under section 505 of the FFDCA if it is not generally recognized to be safe and effective.

is not required. Drug ingredients can similarly be reviewed for inclusion in monographs authorizing their marketing over the counter (OTC monographs) as generally recognized as safe and effective (GRAS/E) for specified conditions of use. Once the monograph is in place, it covers all products that comply with it, and individual premarket review of such products is not required. FDA-regulated products not subject to premarket authorization include dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS). Although premarket authorization does not apply, premarket notification is required in some cases for dietary supplements containing new dietary ingredients,[29] and premarket notifications may be submitted at the option of the manufacturer for GRAS food ingredients.[30]

In all cases, whether subject to premarket authorization or not, FDA-regulated products cannot be marketed unless they satisfy specified statutory requirements. In addition to other such requirements, drugs, biological products and devices must be safe and effective; and foods (including dietary supplements and food additives), color additives, and cosmetics must be safe.[31]

As discussed in the State of the Science section, the Task Force believes that nanoscale materials will present regulatory challenges that are similar to those posed by other new technologies FDA has dealt with in the past, such as biotechnology products, but also some potentially new challenges. The Task Force began its regulatory policy inquiry by reviewing the agency's authorities to meet any unique challenges that may be presented by FDA-regulated products containing nanoscale materials. Although FDA's authorities may be adequate to meet these challenges, in some cases the evolving state of the science regarding nanotechnology may warrant a case-by-case approach to assess whether sufficient evidence exists to show that products satisfy the applicable statutory and regulatory standards.

The Task Force has made recommendations that seek to address the challenges nanoscale materials may present. The guidances the Task Force is recommending would give affected manufacturers and other interested parties timely information about FDA's expectations, so as to foster predictability in the agency's regulatory processes, thereby enabling innovation and enhancing transparency, while protecting the public health.

The very nature of nanoscale materials – their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications – may permit the development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for "combination products"[32] may need to be assessed to ensure predictable determinations

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[29] A "new dietary ingredient" is a dietary ingredient that was not marketed in the United States before October 15, 1994. New dietary ingredients require a premarket notification to FDA unless the ingredient has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered." 21 U.S.C. 350b.

[30] Notifications of a GRAS determination can also be submitted on a postmarket basis.

[31] Under section 351 of the PHS Act, FDA will approve a biologics license application on the basis of a demonstration that, among other things, the biological product that is the subject of the application is safe, pure, and potent. Potency has long been interpreted to include effectiveness. 21 CFR 600.3(s).

[32] A combination product is a product that is a drug-device, drug-biologic, device-biologic, or a drug-device-biologic. The assignment of a "lead center" that will have primary jurisdiction for its regulation is

of the most appropriate pathway for such highly integrated combination products.

Continuing agency efforts to gather together and share scientific knowledge of nanoscale materials, across centers and divisions, will be important to facilitate informed regulatory activity in light of the evolving state of this scientific knowledge. Such coordinated assessment and dissemination of information will enable informed determinations of how best to approach premarket review, including identification of appropriate regulatory pathways for such highly integrated combination products. Among other uses, it will also support assessment of postmarket surveillance of products using nanoscale materials.

As the recommendations below reflect, the Task Force believes communication between regulated entities and the agency early in the product development process, particularly with regard to highly integrated combination products, will help ensure timely consideration of any potentially novel issues that products using nanoscale materials may raise. In addition, to assist the agency to be well-positioned to enable the development and premarket review of such highly integrated combination products, the Task Force recommends that FDA seek public input on the adequacy of agency policies and procedures.

Discussion

The Task Force has considered four broad regulatory policy questions that concern FDA in relation to the presence of nanoscale materials in FDA-regulated products. These questions are:

- Is FDA able to determine whether particle sizes or material features of products extend into the nanoscale range?
- What is the scope of the agency's authority regarding the evaluation of the safety and effectiveness of products containing nanoscale materials?
- Should product labeling declaring the presence or amount of nanoscale materials be either required or permitted?
- Does the use of nanoscale materials in FDA-regulated products raise any issues under the National Environmental Policy Act (NEPA)?

After summarizing the agency's general authorities, we address each question in turn below, taking into account relevant comments submitted to the public docket for the FDA Nanotechnology Task Force's October 2006 public meeting and to the docket opened in response to the ICTA Petition.

Summary of Agency Oversight Authorities by Product Type

Following are concise summaries by product type of certain agency statutory and regulatory

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based on a determination of the "primary mode of action" of the combination product. FDA regulations define the primary mode of action of a combination product as "the single mode of action . . . that provides the most important therapeutic action of the combination product" (21 CFR 3.2(m)) and define therapeutic action or effect to include "any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body" (21 CFR 3.2(k)).

authorities relating to product safety, effectiveness (as applicable), and quality. This discussion is relevant, in particular, to the Task Force's analyses and recommendations with respect to the first and second questions presented above.

New Drugs and Biological Drug Products

Sponsors are required to submit an Investigational New Drug (IND) application to FDA in accordance with 21 CFR Part 312 prior to conducting human clinical studies of most drugs.[33] INDs are required to contain detailed information about the investigational new drug, including chemistry, manufacturing, and controls information, such as information about its active ingredients and structural formula, and pharmacological and toxicological results from studies of the drug in animals. During FDA's review of the data contained in the IND submission, the agency may identify additional information necessary to assure the safety of subjects and assure that the study design is adequate to permit an evaluation of the drug's safety or effectiveness in humans. FDA has the authority to request such additional safety data from the sponsor, including particle size data, when it is needed to support the IND.

After a drug has been adequately studied in humans, the applicant must submit a new drug application (NDA) to obtain approval to market the drug (21 CFR § 314.50). For biological products regulated under section 351 of the PHS Act, an applicant must submit a biologics license application (BLA) (21 CFR § 601.2). Applicants are required to submit in NDAs and BLAs detailed technical information about their products, including chemistry, manufacturing, and controls information, the results of animal pharmacology and toxicology studies, bioavailability data, and extensive data on safety and effectiveness generated in clinical investigations of the drugs in humans.

Applicants may also seek FDA approval of an abbreviated new drug application (ANDA) to market a generic version of a drug for which the agency has previously approved an NDA. ANDAs contain detailed technical information about the product, including chemistry, manufacturing, and controls information, and bioavailability and bioequivalence data, but do not include extensive human data from clinical investigations (21 CFR § 314.94).

During FDA's review of these applications, the agency may call for additional data from the sponsor needed to support the applications, including particle size data, if not supplied in the original application. FDA requests information on particle size when the agency considers such information relevant to determining whether a particular human drug product or class of human drug products is safe and effective. If FDA determines such data are needed for a class of drugs, FDA may issue guidance to applicants recommending that they be submitted in the original application.

Drugs, including biological drugs, are also subject to current good manufacturing practice requirements found in 21 CFR Parts 210 and 211. These requirements govern the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug. They are intended to ensure that the drug meets the safety

[33] A biological product that is subject to licensure under section 351 of the Public Health Service Act (PHS Act) may meet the definition of "drug" under the FFDCA and thus be subject to certain provisions of drug regulation such as the IND regulations.

requirements of the FFDCA, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

In accordance with 21 CFR § 314.70, 21 CFR § 314.97, and 21 CFR § 601.12, after a human drug or biologic product is approved for marketing, the sponsor must notify FDA about each change in each condition established in the approved application. Significant changes require a supplement to the NDA, ANDA, or BLA, and prior FDA approval. Significant changes include a change in drug substance, drug product, production process, quality controls, equipment or facilities that has a substantial potential to have an adverse effect on the drug product. Changes to a product to introduce nanoscale ingredients or processing would trigger change notification chemistry supplements and permit FDA to review and approve the revised formulation. Depending on the change, the resulting product might be considered a new product for which a new approval is needed.

OTC Monograph Drugs

Over-the-counter drug monographs establish the active ingredients and conditions of use for OTC drugs that qualify as generally recognized as safe and effective. Additional active ingredients can be added to an OTC drug monograph in response to a citizen petition (under 21 CFR § 10.30) or a time and extent application for eligibility (under 21 CFR § 330.14) followed by evaluation of data supporting GRAS/E status. Both processes require the submission of safety and effectiveness data. FDA can require data and information to determine if these proposed additional ingredients contain nanoscale materials and, if so, require safety and effectiveness data directly related to particle size to determine whether the ingredient qualifies for inclusion in the monograph.

If a manufacturer does not have an approved NDA for a drug product that has not been marketed in the United States, that manufacturer generally cannot market that drug product unless FDA has published a final OTC monograph that includes the drug product's active ingredient for the intended use.[34] Products containing active ingredients that are already included in a monograph and that bear labeling published in a monograph may be marketed without product-specific premarket authorization. FDA can take various actions however, if the agency learns that a new version of a drug product marketed under an OTC monograph raises a safety or effectiveness concern. A new version that might raise such concerns could be a drug product that contains a monograph ingredient whose particle size has been reduced to the nanoscale range To address this situation, for example, the agency can issue a call for data on the safety and effectiveness of the changed version of the OTC drug ingredient. In addition, under 21 CFR Part 330, FDA can conduct rulemaking to determine whether a nanoscale version of a monograph ingredient should be considered nonmonograph (i.e., not GRAS/E), and therefore to require submission of data in an NDA to establish its safety and effectiveness.

New Animal Drugs and Animal Feed Containing a New Animal Drug

New animal drugs, including new animal drugs for use in animal feed, are regulated under section 512 of the FFDCA and are subject to a premarket authorization process intended to

[34] Under certain circumstances, FDA does not object to the marketing of OTC drugs with active ingredients being considered for inclusion in an OTC monograph as part of the "OTC drug review."

establish the products' safety and effectiveness that is in many respects similar to the process used for new human drugs and biological drug products. An applicant must submit a new animal drug application (NADA) to obtain approval to market the animal drug and the requirements for the contents of NADAs are found in 21 CFR Part 514. Animal drugs must also be manufactured in accordance with current good manufacturing practice requirements found in 21 CFR Part 211. FDA has the authority to require information that will adequately characterize the drug formulation, identify quality-indicating specifications, and ensure that factors affecting the quality, purity, strength and potency are adequately understood and controlled. This authority includes the ability to require the submission of a product's particle size, where the particle size might have an impact on the safety or effectiveness of the animal drug.

Devices

Medical devices are regulated under the FFDCA according to a tiered classification system that is largely based on the degree of risk posed by the product. Devices that are low risk, for which safety and effectiveness are generally well-established, are designated as Class I devices. These device types are subject to general controls, such as labeling, good manufacturing practices and adverse event reporting.

Class II devices are more complex, and carry a higher risk than Class I devices. Before marketing the product, manufacturers are usually required to submit a premarket notification under section 510(k) of the FFDCA (510(k) submission) for FDA review. In a 510(k) submission, manufacturers are required to submit data and other information to demonstrate that their device is "substantially equivalent" with regard to safety and effectiveness to a similar device already legally marketed in the United States. The evidence provided usually consists of pre-clinical testing (such as animal, bench, and analytical testing), and occasionally, clinical data (such as data derived from a study using a patient population with a defined clinical condition).

In some cases, manufacturers may make modifications to Class I or Class II devices after FDA clearance without submitting a new 510(k) submission. FDA provides guidance on when a new 510(k) is needed for a modified device in the guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)."[35] Manufacturers of a commercially distributed Class I or Class II device, for which FDA has granted an exemption from the requirement of a 510(k) submission for the generic type of device, must still make such a submission under certain circumstances, such as when the modified device operates using a different fundamental scientific technology than a legally marketed device in that generic type of device. Accordingly, manufacturers would have to make a submission if use of a nanoscale material were to qualify as a use of a different fundamental scientific technology.

Class III devices are the most complex, high risk devices. These devices are reviewed under a premarket approval application (PMA). In a PMA, manufacturers provide detailed evidence that their device provides a "reasonable assurance of safety and effectiveness." The evidence provided usually consists of pre-clinical testing, and clinical data. Class III PMA devices are subject to a pre-approval manufacturing inspection and require submission

[35] http://www.fda.gov/cdrh/ode/510kmod.pdf

of periodic reports. Any modification to a PMA device and its method of manufacture that could affect safety or effectiveness requires approval by FDA through the submission of a PMA supplement. A PMA might be required for a product otherwise within a general category considered Class I or Class II if the inclusion of nanoscale material raises questions of safety or effectiveness warranting clinical studies.

Manufacturers are required to submit information in sufficient detail to describe the device and its intended use. This includes, for example, information on the chemical composition and physical characteristics of materials that comprise the device. In general, devices must be manufactured in accordance with the Quality System Regulation (21 CFR Part 820).

All clinical evaluations of investigational devices, unless exempt, must have an approved investigational device exemption (IDE) before the study is initiated. An approved IDE is required for "significant risk devices" but not for "nonsignificant risk" devices. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject.

Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Clinical studies of devices that pose a significant risk require both FDA and Institutional Review Board (IRB) approval prior to initiation of the study. FDA approval is obtained by submitting an IDE application to FDA (21 CFR § 812.20). If use of a nanoscale material were to pose a potential for serious risk to health, safety, or welfare of a subject, an IDE would, therefore, be required.

Nonsignificant risk devices are devices that do not pose a significant risk to human subjects. Examples include ultrasonic dental scalers, conventional laparoscopes, culdoscopes, hysteroscopes, and foley catheters. A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study, and sponsors are not required to submit an IDE application to FDA for approval. If the IRB disagrees with the sponsor and determines that the device poses a significant risk, the sponsor must report this finding to FDA.

Guidance on distinguishing between significant risk and nonsignificant risk studies is outlined in the FDA guidance document entitled "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies."[36]

Food Additives and GRAS Food Ingredients

FDA regulates food additives and generally recognized as safe (GRAS) food ingredients under sections 201(s) and 409 of the FFDCA. Under these statutory provisions, any substance added to food "directly or indirectly" is a food additive unless the substance is GRAS for its intended use, is a pesticide, or is otherwise excluded from the definition of a food additive. Food additives must receive premarket approval from FDA in the form of a regulation establishing conditions of safe use. Food additives include those substances added directly to food, substances that may become components of food as a result of their

[36] http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf

use in processing, and components of food contact materials that can reasonably be expected to migrate to food.

Section 409 of the FFDCA and 21 CFR Parts 170 and 171 describe in general terms the information and data necessary to establish the safety of food additives and ingredients. These authorities are supplemented by technical guidance documents providing more specific data recommendations. In addition, FDA may require any other information that it determines during its review is necessary to establish safety.

The specific data that FDA can require to establish the safety of food additives include information on: identity, including physical characteristics such as particle size; the physical or chemical technical effect of the additive; analytical methods for determining the quantity of the substance in food; and the safety of the intended use of the substance. These requirements exist regardless of the physical or chemical characteristics or physical state of the additive. Where appropriate to ensure safety, FDA places limitations on the physical and chemical properties of food additives, which include particle size.

For an approved food additive, FDA publishes a final regulation establishing conditions under which the substance may be safely used. Like an OTC monograph, this rule applies to products that satisfy these conditions. FDA can take various actions however, if the agency learns that a new version of a substance being marketed under a food additive regulation raises safety concerns. A new version that might raise such concerns could be a food additive that contains or may contain nanoscale materials. In such a situation, for example, the agency can issue a call for data on the safety of such a version of the substance. In addition, under 21 CFR Parts 170 and 171, FDA can publish a proposed rule to amend the food additive regulation to address under what circumstances the nanoscale version of the substance may be safely used.

GRAS uses of food ingredients do not require premarket authorization by FDA. Nonetheless, the safety data and information to support GRAS uses of food ingredients must be of the same quality and quantity as data needed to establish the safety of a food additive. In addition, the data must be generally available. Finally, for uses of food ingredients to be GRAS, the safety of the ingredient must be generally recognized by scientists qualified to assess the safety of such substances. As part of its GRAS notice process, FDA can inform manufacturers of what data the agency considers necessary to establish the safety of food ingredients.

Color Additives

FDA regulates color additives under sections 201(t) and 721 of the FFDCA. Generally under these statutory provisions, any substance capable of imparting color to any food, drug, cosmetic, or medical device, or the human body is a color additive that requires premarket approval by FDA in the form of a regulation listing (i.e., approving) the color additive for its intended uses. In addition to being used in compliance with an existing regulation, some color additives may require batch certification by FDA. During the premarket approval process for color additives, FDA reviews detailed manufacturing and analytical data to judge whether postmarket batch certification will be required. In many cases this part of the premarket authorization process requires the sponsor to provide batch samples of the color for analysis by FDA color chemists. The judgment regarding whether a color requires batch

certification is ordinarily based on the expected variation in manufactured color and on the degree of concern that such variation raises regarding the safety of the color additive.

Section 721 of the FFDCA and 21 CFR Part 71 describe in general terms the information and data necessary to establish the safety of color additives. These authorities are supplemented by technical guidance documents providing more specific data recommendations. In addition, FDA can generally require the submission of any data that it determines in its review to be necessary to establish safety. The specific data that FDA can require to establish the safety of a color additive include information on: identity, including physical characteristics such as particle size; analytical methods for determining the quantity of the substance in the finished product and for ensuring the purity and consistency of the manufactured color; and the safety of the color additive under its intended conditions of use. These requirements exist regardless of the physical or chemical characteristics or physical state of the color additive. Where appropriate to ensure safety, FDA places limitations on the physical and chemical properties of color additives, which include particle size.

Once FDA has promulgated a regulation listing a color additive, the regulation applies to products that comply with the rule's conditions. However, FDA can take various actions if the agency learns that a new version of a substance being marketed under a color additive regulation raises safety concerns. A new version that might raise such concerns could be a color additive that contains or may contain nanoscale materials.[37] In such a situation, for example, the agency can issue a call for data on the safety of such a version of the substance. In addition, under 21 CFR Part 71, FDA can publish a proposed rule to amend the listing regulation to address under what circumstances the nanoscale version of the substance may be safely used.

Cosmetics

Section 201(i) of the FFDCA defines a cosmetic as an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap.[38] This definition includes skin-care creams, lotions, hairsprays, perfumes, lipsticks, fingernail polishes, eye and facial makeup, permanent waves, hair colors, deodorants, baby products (e.g., baby powder, baby oil, wipes), bath oils, bubble baths, and mouthwashes, as well as any material intended for use as a component of a cosmetic product. Under the FFDCA, FDA is not given premarket approval authority for cosmetic products and most cosmetic ingredients (other than color additives). However, FDA's mission includes ensuring that cosmetics are safe and properly labeled. FDA pursues this mission through a combination of activities which include inspection of cosmetic manufacturing establishments and enforcement actions for cosmetic products found to be in violation of the "adulteration" (Section 601) and/or "misbranding" (Section 602) provisions of the FFDCA. For example, if a cosmetic bears or contains any poisonous or deleterious substance which

[37] Although adverse events for color additives marketed as stand-alone products or used in conventional foods and cosmetics do not have to be reported to FDA, adverse events for color additives that are components of a drug or device must be reported as part of the adverse event reporting requirements for the finished product.

[38] However, a product that meets the definition for a cosmetic but is intended to affect the structure or function of the body of man will also be subject to regulation as a drug or device.

may render it injurious to users when used under labeled or customary conditions of use, the product is adulterated.

Dietary Supplements

Dietary supplements are regulated under the FFDCA, as amended by the Dietary Supplement Health and Education Act of 1994, or DSHEA. In addition, there are implementing regulations in 21 CFR Parts 101, 119, and 190. As defined in the statute (21 U.S.C. 321(ff)), a dietary supplement is a product other than tobacco that is intended to supplement the diet and that contains one or more dietary ingredients. A dietary ingredient is any one of the following: a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total daily intake; or a concentrate, metabolite, constituent, extract or combination of any of the other types of dietary ingredients. The requirement to contain a dietary ingredient is only one element of the dietary supplement definition. A dietary supplement must also be labeled as such and must be intended for ingestion. Topical products like lotions and ointments cannot be dietary supplements. A dietary supplement must not be represented for use as a conventional food or as a sole item of a meal or the diet. Generally, articles approved as new drugs, licensed as biologics, or authorized for clinical investigation under an IND cannot be marketed as dietary supplements. However, if the product was marketed as a dietary supplement or as a food before such approval, licensing, or authorization under an IND, it may still be marketed as a dietary supplement afterwards.

With one exception, FDA has no authority to require premarket safety testing or premarket submission of safety information for a dietary supplement. The manufacturer of a dietary supplement must notify FDA at least 75 days in advance of marketing a product if it contains a new dietary ingredient,[39] unless that ingredient has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered" (21 U.S.C. 350(b)). The manufacturer must include in the notification the information on which the manufacturer based its conclusion that a dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. However, the nature of the safety information on which the manufacturer may rely is not specified in the law, and there is no requirement that a manufacturer wait for a safety determination from FDA before marketing the product.

Because the majority of dietary supplements do not contain a new dietary ingredient, most dietary supplement safety issues arise in the post-market context. As with conventional foods and cosmetics, a manufacturer may market a dietary supplement without pre-market authorization from FDA. As part of its responsibility to ensure that FDA-regulated products sold in the U.S. are safe and properly labeled, the agency inspects dietary supplement manufacturing facilities and takes action against dietary supplements that are adulterated (21 U.S.C. 342) or misbranded (21 U.S.C. 343).

Because FDA's regulation of dietary supplements is generally post-market, the agency may not know whether particle sizes or material features used in dietary supplement products are in the nanoscale range, unless the agency becomes aware of the use of such sizes and features, for example, from information submitted in a notification or from the product

[39] A new dietary ingredient is an ingredient not marketed in the U.S. before October 15, 1994.

labeling.

Labeling and Advertising Claims for Conventional Foods and Dietary Supplements

In some cases, FDA may become aware of the use of nanoscale materials or features in a dietary supplement or conventional food because of labeling or advertising claims for the product in the marketplace. These could be claims that explicitly reference the presence of nanoscale materials in the product or claims that describe product characteristics or effects derived from the use of nanoscale materials or nanotechnology.

In addition, there are some labeling claims for conventional foods and dietary supplements that require a premarket petition process or a postmarket notification to FDA. For example, health claims (i.e., claims about reducing the risk of a disease or health-related condition) for a conventional food or dietary supplement require premarket review by FDA. The mechanism for requesting a new health claim is a health claim petition under 21 CFR 101.70, requesting that the agency issue a regulation regarding the claim. Health claim petitions must explain the petitioner's basis for concluding that the substance that is the subject of the requested claim is safe, and petitions must also include studies demonstrating that the substance has the claimed risk reduction effect.

For dietary supplements, the FFDCA (Section 343(r)(6)) specifically authorizes the use of labeling claims concerning effects on the structure or function of the body (structure/function claims), claims of general well-being, and claims of a benefit related to a classical nutrient deficiency disease. These claims do not require premarket review, but they do require notification to FDA within 30 days of marketing. Unlike a health claim petition, however, a postmarket notification for a dietary supplement labeling claim under Section 403(r)(6) of the Act need not include safety information about the substance for which the claim is being made or studies demonstrating that it has the effect claimed.

In summary, FDA review of a labeling claim, such as a structure or function claim or health claim, would not necessarily include information related to use of nanoscale materials. Whether the agency would have the opportunity to review such information would depend on whether the nanoscale material was related to the basis for the labeling claim and, if so, whether the information about the nanoscale material was submitted to the agency, e.g., in a health claim petition as required by 21 CFR § 101.70(f), or voluntarily for other types of claims.

Issue: Ability of FDA to Identify FDA-Regulated Products that Contain Nanoscale Materials

Comments

Several comments stressed the importance of identifying the use of nanoscale materials in FDA-regulated products. One comment suggested that companies generally submit information on particle size. Another comment urged FDA to call for data on uses of nanotechnology for foods. Another comment suggested that FDA establish a mandatory premarket notification system for novel uses of nanotechnology and urged FDA to issue

guidance defining “novel use.” Several comments discussed the importance of a clear definition of nanoscale materials in order to eliminate confusion. A few comments stated it was necessary to distinguish between “common” nano-sized food ingredients and those intentionally nano-sized.

Analysis

As discussed in the State of the Science section, although the science of nanotechnology is continuing to evolve, it is known that the size of a particle can affect its properties such that versions of the same substance with differing particle sizes can have different properties, such as their interaction with light (e.g., transparency of lotions). To appropriately assess the safety and, as applicable, the effectiveness of products, it will be important in some cases for FDA, or the manufacturer, to take into account whether the product contains nanoscale materials. FDA’s authority to obtain information on particle size differs depending on whether products are subject to premarket authorization or not. As indicated above, the agency’s authority is comprehensive with regard to products subject to premarket authorization such as drugs, devices, biological products, and food and color additives. FDA's authority is more limited with regard to products that are not subject to premarket authorization, which include cosmetics and dietary supplements.

FDA can require submission of data regarding particle size and other relevant properties when such data are necessary to evaluate the safety or, as appropriate, effectiveness of a product that is subject to premarket authorization. However, the agency might not obtain such information if the manufacturer is uncertain of whether it needs to obtain authorization to market its product or already has authorization to do so (e.g., of whether its product is covered by an existing food or color additive regulation or by an OTC drug monograph). When dealing with products not subject to premarket authorization, the agency has less ability to obtain information about the presence of nanoscale materials.

Recommendations for Consideration

Issue guidance to sponsors regarding identification of the particle size for:

- Products subject to premarket authorization, including OTC drugs (when a new monograph or amendment to a monograph is being proposed), and food and color additives (in petitions to approve new additives or to amend existing approvals); and

- Products not subject to premarket authorization but for which the sponsor is required to provide notice (such as dietary supplements containing certain new dietary ingredients), or may choose to provide notice (such as a GRAS notification).

When warranted, issue a call for data to identify:

- OTC drug products that contain or may contain nanoscale versions of ingredients included in an OTC monograph; and

- Nanoscale versions of previously approved food and color additives.

Issue: Scope of FDA's Authority Regarding Evaluation of Safety

and Effectiveness

Comments

Several comments requested that FDA collect safety information on the use of nanotechnology in regulated products. Most comments stated that there should be disclosure, transparency, and sharing of scientific information. One comment suggested that all existing safety data should be submitted. One comment recommended that FDA request available studies on nano- and micro-scale ingredients to substantiate safety in personal care products. One comment urged cosmetic manufacturers to submit substantiation data voluntarily. Other comments urged obligatory reporting of safety and health problems caused by nanoscale products.

Opinions differed regarding the need to develop a regulatory framework specific to nanotechnology. Most of the comments urged regulation based upon the unique risks of small particle size. One comment, for example, stated that FDA should start with the assumption that nanoscale materials in products behave in a distinct way and, therefore, should be subject to nanospecific paradigms and health and safety testing. On the other hand, many of the comments stated that there was not enough scientific evidence of unique risks posed by products using nanotechnology and therefore disagreed that FDA should establish a distinct regulatory regime for products using nanotechnology. These comments stated that the regulatory pathways currently utilized by FDA based on statutory classification of the products are sufficient to ensure the safety and effectiveness of products using nanotechnology. These comments urged FDA to evaluate products according to consistent, proven safety standards. Still other comments stated the need to address "intentionally produced" nanoscale materials. One comment stressed the need to avoid definitions that failed to distinguish between common, naturally occurring nanoscale food components and those intentionally used components that might, based upon the hazards posed, require modification of existing regulatory frameworks.

Several comments stated that products using nanotechnology should be treated as new products. Some groups wanted all products using nanotechnology to be subjected to safety testing prior to marketing. One comment suggested that use of nanoscale materials could change the regulatory pathway used to ensure safety and that FDA establish criteria for what is "new for legal and regulatory purposes" and "new for safety evaluation purposes."

Some comments focused on the safety standard for products using nanotechnology. One comment suggested that the agency adopt a "reasonable certainty of no harm" standard. Several comments requested guidance on substantiation, one of which recommended that substantiation be based on the "competent and reliable scientific evidence" standard under the Federal Trade Commission Act.

Several comments focused on the process for developing timely and responsible regulations. These comments urged that any regulation to identify and minimize risks should be adopted in an open and transparent process.

One comment stated that FDA has ample legal authority to require food manufacturers to establish safety, substantiate label claims based on sound science, and remove unsafe products from the market.

Analysis

Products Subject to Premarket Authorization

Because nanoscale materials can behave differently than other versions of the same materials, it will be important for FDA to obtain relevant information about the characteristics of products containing nanoscale materials. The guidance recommended in the section above entitled "Ability of FDA to Identify FDA-Regulated Products that Contain Nanoscale Materials" would assist the agency in identifying the particle size and other relevant properties of nanoscale materials in products subject to FDA's review. As stated above, FDA's authority over products subject to premarket authorization is comprehensive and provides FDA with the ability to obtain detailed scientific information needed to assess the safety and, as applicable, effectiveness of products, including relevant effects of nanoscale materials. In some cases, the presence of nanoscale materials may change the regulatory status/regulatory pathway of products. The Task Force believes it is important that manufacturers and sponsors be aware of the issues raised by nanoscale materials and the possible change in the regulatory status/pathway when products contain nanoscale materials.

Recommendations for Consideration

To provide clear guidance to interested parties and to enhance FDA's knowledge base, the Task Force recommends that the agency take the following actions regarding products subject to premarket authorization:

- Issue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety and effectiveness of nanoscale materials in products subject to FDA premarket authorization, including both existing products that are changed to include (or include greater proportions of) nanoscale materials and new products made with nanoscale materials. In addition, the Task Force recommends that FDA seek comment on whether FDA's current policies for determining the appropriate regulatory pathway are optimal for reaching timely and predictable decisions for highly integrated combination products containing nanoscale materials. If commenters believe current policies are not optimal, they would be asked for examples of the kinds of products for which FDA's policies are not optimal and why they are not.

- Issue guidance requesting submission of information on whether and how the presence of nanoscale materials affects the manufacturing process for products subject to premarket authorization, as part of a premarket submission. Relevant information would address situations when the product contains nanoscale materials and when any part of the manufacturing process involves nanoscale materials, even if those materials do not become part of the finished product.

Issue guidance or amend existing guidance to describe what additional or distinct information should be submitted to FDA or generated with regard to the following:

- New food or color additives made with nanoscale materials; and

- Previously approved food or color additives that are now made with nanoscale

materials or to contain greater proportions of nanoscale materials.

Issue guidance describing when:

- A sponsor of a Class I or Class II device, who is otherwise exempt from submitting a 510(k), would need to submit a 510(k) because the presence or amount of nanoscale material would result in the device being outside the scope of the limitations of exemption described in the general provisions of the applicable regulations (see 21 CFR §§ 862.9-892.9);

- A sponsor should submit a new 510(k) for a modification to a previously cleared device that incorporates the use or increased use of nanoscale materials; and

- IRBs, investigators, and industry should seek input from FDA on significant risk/nonsignificant risk decisions regarding investigational devices containing nanoscale materials.

Products Not Subject to Premarket Authorization

Where products are not subject to premarket authorization, manufacturers generally are not required to submit data to FDA prior to marketing, and agency oversight capacity is, therefore, less comprehensive. However, manufacturers are still responsible for ensuring that the products they market are safe. For example, cosmetic manufacturers are required to ensure the safety of their products but are not required to provide safety data to FDA. In light of the evolving state of the science, the Task Force believes an appropriate course of action at this time would be for the agency to work with manufacturers of these products and assist them in identifying data to substantiate the safety of products containing nanoscale materials, including chronic toxicity and other long-term toxicity data as appropriate.

Recommendations for Consideration

We recommend the following regarding products not subject to premarket authorization:

- Issue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety of nanoscale materials in products not subject to premarket authorization. The notice would address both new products made with nanoscale materials and existing products that are changed to include or include greater proportions of nanoscale materials.

- Issue guidance or amend existing guidance to describe what additional or distinct information should be submitted to FDA or generated with regard to:

    - The use of nanoscale materials in food ingredients for which a GRAS notification is submitted or the reduction of particle size into the nanoscale range for food ingredients for which an earlier notification had been submitted and not objected to by FDA; and

    - The use of nanoscale materials in new dietary ingredients.

- Issue guidance recommending manufacturers consider whether and how the presence

of nanoscale materials affects the manufacturing process. Relevant considerations would include both situations when the product contains nanoscale materials and when any part of the manufacturing process involves nanoscale materials, even if those materials do not become part of the finished product.

- Issue guidance describing safety issues that manufacturers should consider to ensure that cosmetics made with nanoscale materials are not adulterated.

- Issue guidance on whether a dietary ingredient modified to include nanoscale materials or include a greater proportion of nanoscale materials would still qualify as a dietary ingredient under 21 U.S.C. 321(ff) (1), and on when the reduction in size into the nanoscale range of an "old" dietary ingredient might trigger the notification process required for a new dietary ingredient on the basis of the presence or amount of nanoscale materials.

Issue: Permissible and Mandatory Labeling

Comments

Several comments urged the disclosure in labeling of the presence of nanoscale materials in FDA-regulated products. A few stressed the importance of clear definitions of "nanoengineered materials and nanotechnology" to enable such disclosure. One group recommended that FDA enforce warning label requirements for cosmetics.

Analysis

Consumers are increasingly exposed to information about nanotechnology products, but they may not always understand whether the use of nanotechnology has a significant effect on the products they purchase. As with many other new technologies, the use of nanotechnology does not mean that a product's safety or effectiveness is necessarily increased, decreased, or affected in any way. As the comments reflect, consumers may have questions regarding the use of nanotechnology for products regulated by FDA. Whether information on such use must be included in product labeling, or can voluntarily be included, depends on whether its inclusion is required or permitted under the FFDCA.

The FFDCA requires that labeling of FDA-regulated products be truthful and not misleading. Labeling must include material information, including with respect to consequences which may result from the use of the product under the conditions of use prescribed in the labeling or under customary or usual conditions of use. The risk information contained in prescription drug labeling is an example of material information. For foods, information about the characteristics of the food can be material, such as nutritional, organoleptic (e.g., taste, smell, or texture), or functional (e.g., storage) properties. If labeling is false or misleading, the product is "misbranded" and cannot be marketed.

For products subject to premarket authorization, the agency generally considers on a case-by-case basis as part of marketing authorization whether labeling contains adequate information to support the safe and, as applicable, effective use of the product. Labeling for products not subject to premarket authorization (for example, cosmetics) also must include material information and not include false or misleading information. Otherwise, these

products would be misbranded. If FDA determined that a particular use of a specific nanoscale material, or the use of nanoscale materials more generally, was a material fact for a category of products, FDA could amend its regulations to require, for example, that all members of that category of products include labeling regarding such use of nanoscale material.

If disclosure of information on the use of nanoscale materials is not material (and, therefore, is not required to be included in the product labeling), the manufacturer may still be able to include such information, as long as the information is not false or misleading. However, because claims regarding the use of nanoscale materials might be misleading and, therefore, misbrand a product, the Task Force would recommend encouraging manufacturers to consult with the agency concerning such labeling to avoid misbranding the product.

Recommendations for Consideration

Because the current science does not support a finding that classes of products with nanoscale materials necessarily present greater safety concerns than classes of products without nanoscale materials, the Task Force does not believe there is a basis for saying that, as a general matter, a product containing nanoscale materials must be labeled as such. Therefore the Task Force is not recommending that the agency require such labeling at this time. Instead, the Task Force recommends that the agency take the following action:

- Address on a case-by-case basis whether labeling must or may contain information on the use of nanoscale materials.

Issue: National Environmental Policy Act

Comments

No comments were submitted to the Task Force's docket or to the docket for the ICTA Petition regarding NEPA obligations.

Analysis

NEPA requires federal agencies to assess the environmental impacts of "major federal actions" and to ensure that the interested and affected public is informed of environmental analyses. Agencies may prepare an environmental assessment (EA) or environmental impact statement (EIS), as appropriate. Agencies can also establish categorical exclusions for categories of major federal actions that have been determined not to individually or cumulatively have a significant effect on the human environment. However, agency procedures must also provide for those circumstances where a normally excluded action may have a significant environmental effect. Examples of such "extraordinary circumstances" are identified in FDA's regulations and include actions for which available data establish that there is the potential for serious harm to the environment and actions that adversely affect an endangered, threatened, or otherwise specially protected species.

Many FDA regulatory actions constitute major federal actions, including: actions to approve or withdraw applications to market new drugs and biological products; actions to approve or prohibit or otherwise restrict the use of a substance in food, or food packaging; and actions

on premarket notifications and premarket applications for devices. Under FDA's regulations, many of these actions can qualify for a categorical exclusion.

The agency requires applicants and petitioners to submit an EA or a claim of categorical exclusion when requesting agency action. An EA must address the relevant environmental issues and contain sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Agency guidance provides recommendations for preparation of EAs and the making of categorical exclusion claims. The science related to the environmental implications of nanoscale materials is evolving. In some cases, the presence of nanoscale materials may warrant a closer look at potential environmental impacts of an FDA-regulated product. Such products may not qualify for a categorical exclusion or an extraordinary circumstance may exist.

As knowledge of nanoscale materials increases, it may be productive for the agency to develop or amend agency NEPA guidance to address expressly nanoscale materials or certain types of nanoscale materials. In light of the current, evolving state of scientific knowledge regarding nanoscale materials, however, the Task Force recommends a case-by-case approach at this time to assessing NEPA requirements for products using these materials, and coordination across the agency to enable consistent determinations informed by the most current science.

Recommendations for Consideration

We recommend that the agency take the following actions:

- Take into account, on a case-by-case basis, whether an FDA-regulated product containing nanoscale materials qualifies for an existing categorical exclusion and whether extraordinary circumstances exist.

- Designate a lead in the agency to coordinate the agency's approach to its obligations under NEPA regarding nanotechnology.

FDA NEWS RELEASE

Media Inquiries: Christopher Kelly, 301-827-6242, Christopher.kelly@fda.hhs.gov**,**
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Consumer Inquiries: 888-INFO-FDA

FDA Nanotechnology Report Outlines Scientific, Regulatory Challenges

The U.S. Food and Drug Administration (FDA)'s Nanotechnology Task Force today released a report that recommends the agency consider developing guidance and taking other steps to address the benefits and risks of drugs and medical devices using nanotechnology.

"Nanotechnology holds enormous potential for use in a vast array of products," said Commissioner of Food and Drugs Andrew von Eschenbach, M.D., who endorsed the Task Force Report and its recommendations on July 23, 2007. "Recognizing the emerging nature of this technology and its potential for rapid development, this report fosters the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials."

Scientists and researchers increasingly are working in the nanoscale, creating and using materials and devices at the level of molecules and atoms—1/100,000th the width of a human hair.

The FDA's Task Force Report on Nanotechnology addresses regulatory and scientific issues and recommends FDA consider development of nanotechnology-associated guidance for manufacturers and researchers. The Task Force was initiated by Commissioner von Eschenbach in 2006.

The Task Force reports that nanoscale materials potentially could be used in most product types regulated by FDA and that those materials present challenges similar to those posed by products using other emerging technologies. The challenges, however, may be complicated by the fact that properties relevant to product safety and effectiveness may change as size varies within the nanoscale.

The report also says that the emerging and uncertain nature of nanotechnology and the potentially rapid development of applications for FDA-regulated products highlight the need for ensuring transparent, consistent, and predictable regulatory pathways.

Anticipating the potential for rapid development in the field, the report recommends consideration of agency guidance that would clarify, for example, what information to give FDA about products, and also when the use of nanoscale materials may change the regulatory status of particular products. As with other FDA guidance, draft guidance documents would be made available for public comment prior to being finalized.

In addition, the report says the FDA should work to assess data needs to better regulate nanotechnology products, including biological effects and interactions of nanoscale materials. The agency also should develop in-house expertise and ensure consideration of relevant new information on nanotechnology as it becomes available, according to the report. FDA should evaluate the adequacy of current testing approaches to assess safety, effectiveness and quality of nanoscale materials.

FDA and 22 other federal agencies are part of the National Nanotechnology Initiative, a federal research and development program established to coordinate the multi-agency efforts in nanoscale science, engineering, and technology.

For more information:

FDA Nanotechnology Report

Report PDF www.fda.gov/nanotechnology/taskforce/report2007.pdf

Report HTML www.fda.gov/nanotechnology/taskforce/report2007.html

Consumer Article www.fda.gov/consumer/updates/nanotech072507.html

National Nanotechnology Initiative
http://www.nano.gov/

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FDA Nanotechnology Task Force Report Outlines Scientific, Regulatory Challenges

Fact Sheet

Nanotechnology is changing the way that many FDA-regulated products will be made. To further its mission of promoting and protecting the public health, FDA will work to clarify what information will be needed in its efforts to oversee products that contain nanoscale materials –those created at sizes as small as 1/100,000th of a human hair**.**

The Food and Drug Administration's Nanotechnology Task Force report released in July 2007 addresses the science and regulatory needs to regulate drugs, medical devices and other products built on the nanoscale.

- Nanotechnology may provide new drugs that are able to reach specific areas of the body more effectively and at safer doses.

- "Nanomedicine" includes development of tiny sensors that detect disease markers in the body far earlier than existing diagnostic methods, and incredibly small pumps capable of delivering medications precisely to the cells and tissues that need them.

- Other examples of nano-products in development include disease imaging tools and food packaging that further extends shelf life.

FDA Commissioner, Dr. Andrew C. von Eschenbach says "Nanotechnology holds enormous potential for use in a vast array of products. Recognizing the emerging nature of this technology and its potential for rapid development, this report fosters the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials."

The Task Force reported that the potential use of nanoscale materials includes most product types regulated by FDA and that those materials present regulatory challenges similar to other emerging technologies. The Task Force recognizes, however, that product safety and effectiveness can change as size goes up or down within the nanoscale, adding additional complexity to the product review.

The emerging and uncertain nature of nanotechnology and the potential for rapid development of FDA-regulated products using this particular technology make it all the more important that in regulating nanotechnology FDA follow its transparent, consistent, and predictable process. The report recommends:

- Consideration of guidance that would clarify what information manufacturers should give FDA about products, and also when the use of nanoscale materials may change the regulatory status of particular products.

- That manufacturers contact the FDA early in the product development process. In addition, the report recommends that the agency should assess data needs for regulated nanotechnology products, including biological effects and interactions of nano-particles.

- That FDA develop in-house expertise and ensure the consideration of new information on nanotechnology as it becomes available. FDA also should evaluate current testing approaches to assess the safety, effectiveness, and quality of nanoscale materials.

FDA and 22 other federal agencies are part of the National Nanotechnology Initiative, a federal research and development program established to coordinate the multi-agency efforts in nanoscale science, engineering, and technology.

For more information:
National Nanotechnology Initiative
http://www.nano.gov/

FDA Consumer Information:
http://www.fda.gov/consumer/updates/nanotech072507.html
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CDER Perspective on Nanotechnology

Nakissa Sadrieh, Ph.D.

Associate Director for Research Policy and Implementation

OPS/CDER/FDA

Houston, March 2008

Outline

- Applications of nanotechnology in CDER products
  - Already approved products
  - Anticipated products
- Evaluation of nanotechnology-based drug applications: key aspects of their regulatory review.

Impact of nanotechnology on already marketed CDER products

- Sunscreens
  - Nanoscale TiO2 and ZnO
- Reformulations of previously approved products
  - Nanoemulsions
  - Nanocrystal colloid dispersions

Currently marketed sunscreens formulated with nanoparticles

(RED) PRODUCTS CONTAIN MANUFACTURED NANOPARTICLES

PRODUCT	MANUFACTURER	NANO CONTENT CLAIM
Applied Therapeutics™	Applied Therapeutics™	Others claim nano content
Bebe/Enfant High Protection SPF 50	Mustela	Others claim nano content
Blue Lizard® BABY	Crown Laboratories, Inc.	Manufacturers claim nano content
Blue Lizard® Regular	Crown Laboratories, Inc.	Others claim nano content
Blue Lizard® Sensitive	Crown Laboratories, Inc.	Manufacturers claim nano content
Chemical-Free Sunscreen SPF 15	Burt's Bees® Inc.	Manufacturers claim nano content
Cotz SPF 58	Fallene	Others claim nano content

Friends of the Earth

Nanotechnology & Sunscreens: *A Consumer Guide for Avoiding Nano-Sunscreens*

BRAND	MANUFACTURER	NANO CONTENT CLAIM
Daily Sun Defense SPF 20	SkinCeuticals®	Others claim nano content
IS Clinical SPF 20 Moisturizing Treatment Sunscreen	nnovative® Skincare	Others claim nano content
Kids Tear Free SPF 30	Banana Boat®	Others claim nano content
Lips 'n Face Protection Creme and Sunblock Creme	Dermatone® Laboratories	Others claim nano content
Physical UV Defense SPF 30	SkinCeuticals®	Others claim nano content
Rosacea Care Sunscreen "30"	Rosacea Care.	Manufacturers claim nano content
Solar Rx SPF 30+ Nano-Zinc Oxide Sunblock	Keys Soap	Others claim nano content
Soltan® Facial Sun Defence Cream - Optisol®	Boots® and Oxonica® Ltd.	Others claim nano content
Spectra3 SPF 50	Coppertone®	Others claim nano content
SPF 20 Sunscreen Powder	Innovative® Skincare	Others claim nano content
Sport UV Defense SPF 45	SkinCeuticals®	Others claim nano content
Sunscreen Plus Clear Zinc SPF30+	Cancer Council Australia	Manufacturers claim nano content
SunSense™ SPF 30+ Sunscreen	NuCelle® Inc.	Manufacturers claim nano content
TiO2 Automotive Sunscreen*	Nano Chemical Systems Holdings, Inc.	Manufacturers claim nano content
Ultimate UV Defense SPF 30	SkinCeuticals®	Others claim nano content
UV Pearls	Sol-Gel Technologies	Manufacturers claim nano content
ZinClear™ Nano Zinc Oxide	Advanced Nanotechnology Limited	Manufacturers claim nano content

Currently marketed prescription drugs with nanoscale particles

Product	Type of nanoparticle	Indication	Particle size
Magenvist	Gadolinium dimeglumine	MRI contrast agent	<1 nm
Feridex	Superparamagnetic Iron Oxide	MRI contrast agent	120-180 nm
Rapamune	Nanocrystal/Sirolimus	Immunosuppressant	100-1000nm
Emend	Nanocrystal/Aprepitant	Antiemitic	100-1000 nm
TriCor	Nanocrystal/Fenofibrate	Hypolipidemic	
Megace ES	Nanocrystal/Megesterol Acetate	Appetite enhancer	
Doxil	Liposome/Doxorubicin	Antineoplastic	~ 100 nm
AmBisome	Liposome/Amphotericin	Antifungal	
Diprivan	Liposome/Propofol	Anesthetic	
Abraxane	Albumin-coated nanoparticles	Antineoplastic	~ 130 nm
Definity	Lipid coated gas particles	Echography contrast agent	

Impact of nanotechnology on future CDER products: DRUG DELIVER SYSTEMS

- Targeted therapy
  - Minimize drug use; lesser frequency of drug use
  - Enhance safety profile
- Novel dosage forms (such as use of electrical currents or high velocity propulsion for transdermal delivery)
  - Enhanced patient compliance
  - Controlled or sustained release
- Multifunctional particles
- Protection of associated drug against enzymatic and chemical degradation
- Small particles, large surface area
  - High drug entrapment efficiency due to large surface area
  - Enhanced bioavailability
  - Access to less accessible sites

Drug delivery: cost benefits

- Extend lifespan of product by reformulating through novel delivery system
- Enhance effective patent protection
- Drug delivery formulation research is low-cost compared to drug discovery for NME
- Minimizing use of expensive drugs to reduce cost of product

Proposed functions for nanoparticles in drugs

- Platforms or carriers for insoluble or poorly soluble drugs
  - Improve PK properties
- Targeting
- Multifunctionality
  - Serve as scaffolding to attach chemical moieties

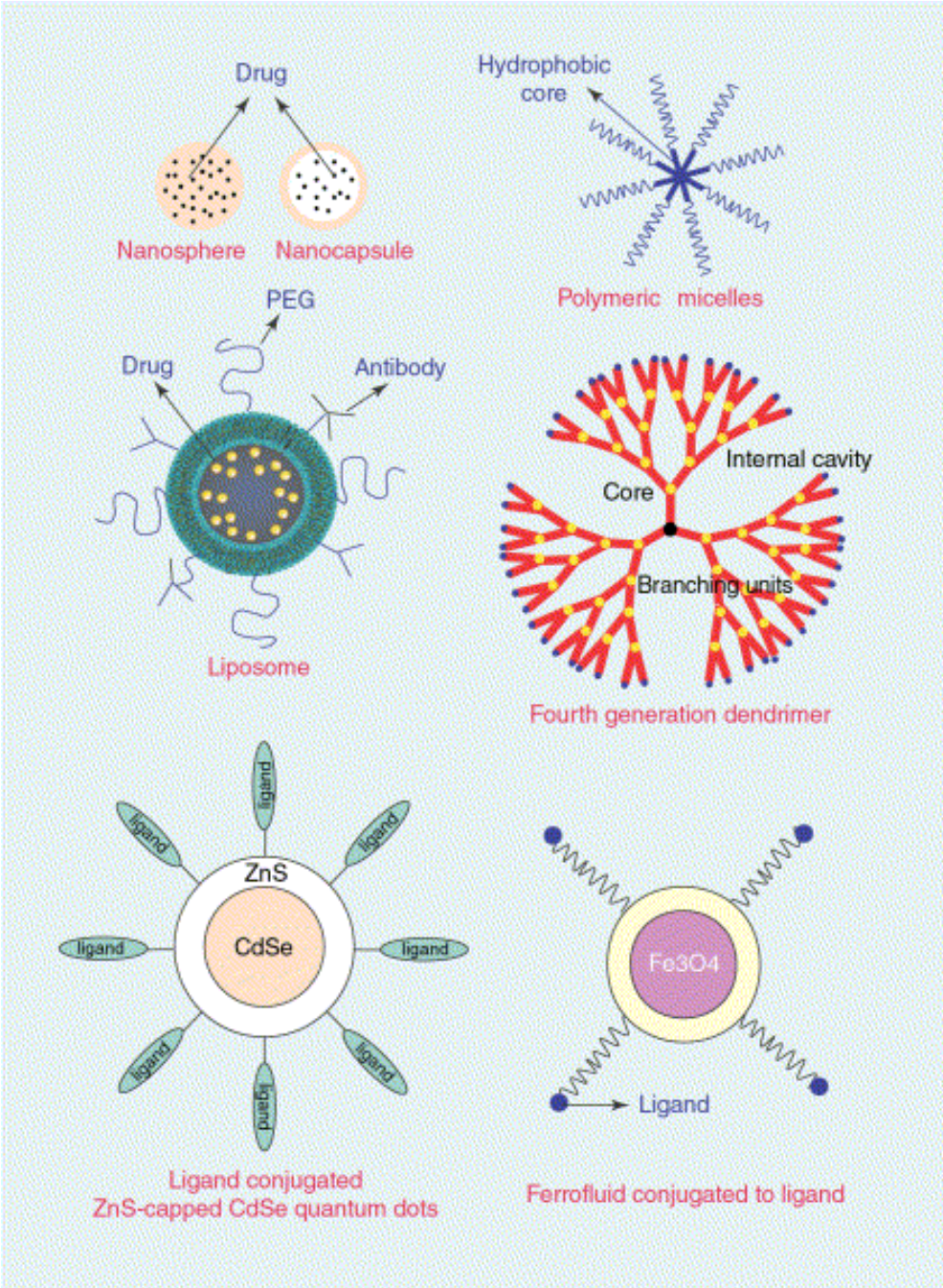
Reported advantages of nanoparticles in drug products

- Targeting
  - Passive (leaky vasculature)
  - Active (receptor ligands)
  - Increase drug concentration at site of action
  - Decrease systemic exposure to drug
  - Lower toxicity profile
- Serve as scaffolding to attach chemical moieties
  - Multifunctional molecules
  - Alteration of surface properties (PEG) to increase solubility or decrease clearance.

Nanotechnology-based drug delivery systems

Sahoo and Labhasetwar, DDT, 2003

- polymeric biodegradable nanoparticles
- ceramic (inorganic) nanoparticles
- polymeric micelles (amphililic block copolymers)
- liposomes
- dendrimers
- nanocrystals (Quantum dots) for diagnostics applications and imaging
- magnetic nanoparticles (iron oxide for MRI)



Drug Discovery Today

Polymeric biodegradable nanoparticles

- Nanoparticles are solid or colloidal particles 10-1000 nm in size.
- Drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated in nanoparticle matrix.
- Nanoparticles are obtained and include:
  - nanospheres (matrix system with drug dispersed), or
  - nanocapsules (vesicular systems with drug confined to a cavity).
- Advantages:
  - Small size; enhanced penetration
  - Sustained release through biodegradable materials

Ceramic nanoparticles

- Inorganic (silica, alumina, titania) molecules with entrapped biomolecules
  - Very low size (less than 50 nm) help bypass RES
  - Biologically compatible
  - Surfaces can be modified for targeting in vivo
  - Drug-doped nanoparticles are relatively stable

Polymeric micelles

- Amphiphilic block copolymers which can self associate to form micelles in aqueous solution
  - Thermodynamically stable in physiological solutions-prolonged systemic circulation and minimal RES uptake (due to small size and hydrophilic shell).
  - Narrow size distribution (less than 100 nm)
  - Useful for the systemic delivery of water-insoluble drugs which are partitioned in the hydrophobic core of the micelles and the outer hydrophilic layers-forms stable dispersion in aqueous media and can be administered intravenously.
  - Can be enhanced by conjugation of targeting ligands.

Liposomes

- Small unilamellar vesicles
  - Single lipid layer, 25-50 nm
- Large unilamellar vesicles
  - Single lipid layer
- Multilamellar vesicles
  - Several lipid layers
- Can be surface modified
  - with PEG to enhance circulation time
  - With antibodies or ligands for targeting

Dendrimers

- Macromolecular compounds around inner core
- Nanometer size range and monodisperse
- Can be functionalized with drug molecules or loaded in the interior

Nanocrystals

- Quantum dots
  - Crystalline core with insulating outer shell.
  - Absorb light at wide range of wavelengths.
  - Emit light of a wavelength depending on size of crystals.
  - Can be functionalized
  - Used for diagnostic purposes.

Applications of nanoparticles in drug development

- Cancer therapy
- Imaging
- Delivery of vaccines
- Delivery of targeted antibiotics

Areas that can significantly impact the evaluation of nanomaterial-containing products

- Product quality assessment studies
  - Characterization
  - Quality control
  - Manufacturing
- Product safety assessment studies
  - Biodistribution
  - Clearance
  - Metabolism
  - Toxicology

Characterization needs

- Development of appropriate tools and methodologies to
  - Adequately assess product chemistry and unique characteristics of product (complete formulation)
  - Enhance quality control measures
  - Produce consistent formulations with low batch-to-batch variability
  - Link product quality to performance

What is safety?

- **Dose that does not result in toxicity**
  - Relative safety: risk-benefit ratio?
  - Depends on:
    - Disease (cancer vs. obesity)
    - Target population (pediatric, pregnant women, some form of impairment)
- How do we measure safety?
  - Clinically
  - Preclinically

Features of nanoparticles that could be analyzed in drug products

- Size
  - Primary particle size
  - Aggregation/agglomeration state
  - 2D and 3 D distribution
  - Particle size distribution
- Chemical composition
  - Element identification and distribution
  - Crystal form
  - Surface composition; surface charge
  - Reactivity

Purpose of preclinical safety assessment

- Traditionally to answer questions that cannot be answered with clinical studies:
  - Can women of child-bearing age take the drug?
  - Might there be harm to the fetus?
  - Will prolonged exposure result in cancer?
- To guide clinical studies; will depend on:
  - Formulation
  - Route of administration
  - Clinical population

Purpose of preclinical studies

- Evaluate toxicities that cannot be measured in clinical studies
  - Genotoxicity
  - Carcinogenicity
  - Histopathology
  - Developmental toxicity
- To help establish a starting dose for the first-in-man clinical studies.

What tools are used to screen for safety?

- Animal toxicology studies
  - Multiple species
  - 3 doses
  - Multiple endpoints measured
- Clinical studies
  - Healthy volunteers
  - Patients
  - Organ impaired and at risk populations

Are there other tools needed to measure safety?

- Input is needed from the scientific community to address this question.
  - What do our current tests miss?
  - What would additional tests measure?
  - Would additional tests only improve our evaluation of nanotechnology-based therapeutics or would they add value to all drug product applications?

Collaborative research with NCTR

substance	description	When initiated	Study leader	FDA collaborators	Other collaborators
TiO2	Dermal penetration and toxicity in mice (also Qdots)	2004	P Howard, NCTR	B Bronaugh, CFSAN	NTP/NIEHS
TiO2	Dermal penetration in minipigs	2006	N Sadrieh, CDER	L Buhse, CDER; P Howard, NCTR; N Gopee, NCTR	
TiO2	Dermal penetration in humans	2006	S Miller, CDRH	N Sadrieh, L Buhse, CDER; P Howard, NCTR; J Beer, CDRH	NIH, NCI/NCL
Nano silver	Distribution and toxicity in mice	2008	M Boudreau, NCTR	Nominated to NTP by FDA	NTP/NIEHS, NIST
Nano gold	Distribution and toxicity in mice	2008	N Gopee, NCTR	Nominated to NTP by FDA	NTP/NIEHS, NIST, NCI/NCL

Additional research projects in CDER

- Characterization of nanoparticles in marketed sunscreens (to address Citizen Petition).
- Toxicity of select nanoparticles; correlation of in vitro findings with in vivo results.
- Collaborators: NIST, NCL/NCI, CDRH.

Challenges ahead

- Define the existing scientific gaps:
  - Identify the critical parameters for various types of nanoparticles that may be used in drug products.
  - Identify and develop appropriate methods to characterize these specific nanoparticle parameters.

Challenges ahead (continued)

- Conclude on the appropriateness of existing methods to assess safety.
- Identify if additional safety assessment tools need to be developed and what should these new assays measure.

Conclusions

- Identify the scientific gaps in nanoparticle-based drug development.
- Define the steps to help overcome these gaps.
- Identify the appropriate groups that can help to address the issues.
- Establish collaborations.

DAY 1 TOPIC 2:

Lead in Pharmaceutical Products

November 2006

Guidance for Industry

Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy

Additional copies are available from:
Office of Plant and Dairy Foods, HFS-300
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
(Tel) 301-436-2022
http://www.cfsan.fda.gov/guidance.html

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
November 2006

Guidance for Industry [1]

Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy

This guidance document represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any

person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate telephone number listed on the title page of this guidance.

I. Introduction

This guidance provides a recommended maximum lead level of 0.1 ppm in candy[2] likely to be consumed frequently by small children. FDA considers the recommended maximum lead level to be achievable with the use of good manufacturing practices in the production of candy and candy ingredients and to be protective of human health. For additional discussion of the background and rationale underlying this recommended level, see "Supporting Document for Recommended Maximum Level for Lead in Candy Likely To Be Consumed Frequently by Small Children."

In addition to announcing the recommended maximum lead level, FDA as explained below, is rescinding the previous 0.5 ppm guideline for considering enforcement action against candy products likely to be consumed frequently by small children. FDA is prepared to take enforcement action against any candy product containing lead at levels that may pose a health risk. Further, FDA is reiterating its enforcement policy toward the use of lead-based ink on candy wrappers as originally stated in its 1995 letter to the industry on this subject.

FDA considers the issuance of this guidance to be a prudent public health measure consistent with the Agency's policy of reducing lead levels in the food supply to reduce consumers' lead exposure to the lowest level that can be practicably obtained.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Discussion

A. Recommended Maximum Level for Lead in Candy Likely To Be Consumed Frequently by Small Children

FDA is recommending that lead levels in candy products likely to be consumed frequently by small children not exceed 0.1 ppm because such levels are achievable under good manufacturing practices and would not pose a significant risk to small children for adverse effects. This recommended maximum level of 0.1 ppm for lead in candy likely to be consumed frequently by small children is consistent with the FDA's longstanding goal of reducing lead levels in the food supply to reduce consumers' lead exposure to the lowest level that can be practicably obtained. This recommendation is further discussed in the supporting document for this guidance noted above.

B. Enforcement Policy for Lead in Candy Likely To Be Consumed Frequently by Small Children

Because it is no longer regarded as consistent with the agency's policy of reducing lead levels in the food supply to reduce consumers' lead exposure to the lowest level that can practically be obtained FDA is rescinding the guidance it provided in the 1995 letter that stated that, where frequent consumption of candy products by small children could be anticipated, FDA would consider taking regulatory action against candy with lead levels that exceed 0.5 ppm.

FDA is now prepared to take enforcement action against any candy product containing lead at levels that may pose a health risk. FDA intends to consider several factors in bringing enforcement actions regarding lead in candy, including the level of lead present, the best available consumption data, and the lead exposure that would result from consumption of the product.

C. Enforcement Policy for Use of Lead-Based Inks on Candy Wrappers

FDA is reiterating in this guidance that FDA's policy toward the use of lead-based ink on candy wrappers remains as stated in its 1995 letter to the industry on this subject:

> Generally speaking, if lead derived from a lead-based printing ink is found on the portion of the package that directly contacts food or, if such lead could be expected to migrate into the packaged food, the product would likely be regarded as being in violation of the Federal Food, Drug, and Cosmetic Act. Use of the printing ink only on the outer (non-food contact) surface of the package does not ensure that it will not contaminate the food.

Suitable non-lead-based printing inks[3] are widely available for use in food packaging, and we continue to strongly urge all candy manufacturers, including those whose products are offered for import into this country, to refrain from the use of lead-based printing inks on their packaging materials.

In addition, the use of lead-based printing inks on candy wrappers may subject a firm to regulatory action by the U.S. Consumer Product Safety Commission under the Federal Hazardous Substances Act (see Letter to US candy importers - July 9, 2004 (PDF) and Letter to candy producers in Mexico (English version) - July 12, 2004 (PDF) for additional information). Furthermore, the use of lead or lead-based inks in or on packaging, including candy wrappers, is subject to state Toxics in Packaging legislation which has been enacted in nineteen U.S. states, (see Toxics in Packaging Clearinghouse Fact Sheet (PDF) for additional information).

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[1] This guidance has been prepared by the Office of Plant and Dairy Foods in the Center for Food Safety and Applied Nutrition (CFSAN) at the U.S. Food and Drug Administration.

[2] We have included within the broad category of candy, "Mexican-style" candy. "Mexican style" refers to candy which contains ingredients popular in Mexico, such as chili and tamarind,

which are not typically found in domestic candy in the U.S. Within the category of "Mexican-style" candy, we have included powdered snack mix products, which are generally made in Mexico and typically contain combinations of salt, chili powder, sugar and flavoring. These products, popular with children and adults, may be sold alongside of candy in retail outlets, and can be consumed directly from the container like candy, as well as being sprinkled onto fruits and vegetables or in beverages.

[3] Non-lead based printing inks may contain incidental lead at trace levels, e.g., < 0.001%, but, do not contain intentionally added lead as would for example lead chromate inks, which can contain > 2% lead.

Supporting Document for Recommended Maximum Level for Lead in Candy Likely To Be Consumed Frequently by Small Children October 2006

Guidance for Industry: Letter to Manufacturers, Importers, and Distributors of Imported Candy and Candy Wrappers June 13, 1995

Consumer Product Safety Commission: Letter to U.S. Candy Importers (available in PDF) July 9, 2004

Consumer Product Safety Commission: Letter to Candy Producers in Mexico (available in PDF) July 12, 2004

Toxics in Packaging Clearinghouse Fact Sheet (available in PDF) January 2005

This document supercedes "Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy," December 2005

November 2006

Supporting Document for Recommended Maximum Level for Lead in Candy Likely To Be Consumed Frequently by Small Children

[Docket No. 2005D-0481]

U.S. Department of Health and Human Services
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I. Introduction

The purpose of this document is to further present the background and rationale for FDA's recommended maximum lead level in candy likely to be consumed frequently by small children. The 0.1 parts per million (ppm) recommended maximum lead level in candy described herein is included as a part of the 2006 updated FDA guidance on lead in candy entitled "Lead in Candy Likely To Be Frequently Consumed by Small Children: Recommended Maximum Level and Enforcement Policy." FDA considers the recommended maximum lead level to be achievable and to be protective of public heath.

II. Overview of FDA Activities Addressing Lead in Food

Lead is a naturally occurring element whose toxicity in humans has been documented throughout history.

Lead is widely present in our environment due to its natural occurrence and human activities that have introduced it into the general environment such as the use of leaded gasoline. Because lead may be present in environments where food crops are grown and animals used for food are raised, various foods may contain unavoidable but small amounts of lead that do not pose a significant risk to human health.

However, foods may become contaminated with lead if they are grown, stored or processed under conditions that could introduce larger amounts of lead into the food, such as when a root crop is grown in soil that has been contaminated from the past use of leaded pesticides on that acreage. Under such conditions, the resulting contamination of the food may pose a health risk to consumers.

FDA first recognized the need to control potential lead exposure from food in the 1930s. The earliest actions of the agency focused on limiting the potential for lead to become a component of food as a consequence of intentional uses of lead containing substances in agriculture and food processing, e.g., lead-based pesticides and lead containing solder in food cans. (Ref. 1)

During the 1970s and 1980s studies were published documenting adverse effects of lead in children at lower blood lead levels than had been previously established. In 1979, FDA stated that it intended to expand its programs to monitor and reduce lead levels in the food supply with the objective of reducing consumer's lead exposure to the lowest level that can be practicably obtained. (Ref. 2)

The goal of limiting lead contamination of food was facilitated by the development and implementation of the use of welded (non-soldered) food cans during the 1980s. This development and the concurrent prohibition of the use of lead containing gasoline in the U.S. are largely responsible for dramatic decreases in measured lead levels in the U.S. diet beginning

in the 1980s. (Ref. 3)

FDA's past and current activities intended to reduce or limit lead levels in food have addressed pesticides, lead glazed ceramic ware and other house wares, bottled water, wine, food cans, food additives, candy and candy wrappers.

III. FDA Actions Addressing Lead in Candy and Candy Wrappers

Candy products were not known to be a significant food source of lead until 1994, when California authorities found that an imported candy product from Mexico was contaminated with lead that had migrated into the candy from lead-based ink used in the candy's packaging. The package was poorly designed such that its inner coating did not maintain its structural integrity, allowing lead-based ink in the outer package layer to migrate into the candy.

Subsequently, FDA began testing other candy products with lead-based printing inks on their packaging to determine whether lead from the ink was migrating into the candy. In its testing, FDA discovered that, apart from any consideration of the wrapper as source of the lead, some imported candy products from Mexico contained higher lead levels than were typically found in domestic candy products. As discussed below, FDA determined that the higher lead levels were largely associated with certain ingredients used in these imported candy products.

Prompted by these findings, in 1995 FDA issued a letter entitled "Letter to Manufacturers, Importers, and Distributors of Imported Candy and Candy Wrappers," (the 1995 letter), addressing its concerns about lead in candy derived from both candy wrappers and candy ingredients.

Concerning lead in candy derived from sources other than the wrapper, e.g., lead from candy ingredients, FDA advised manufacturers, importers, and distributors of imported candy, that where frequent consumption of candy products by small children could be anticipated, the agency would consider taking regulatory action against candy with lead levels that exceeded 0.5 parts per million (ppm). The 0.5 ppm guideline was, at that time, equivalent to the Food Chemicals Codex (FCC) specification for lead in sucrose (sugar), the main ingredient in many candy products.[1]

Many candy products contain sugar or chocolate as principal ingredients. Sugar (sucrose) is made by a process, i.e., re-crystallization, which when carried out under good manufacturing practices, typically results in low parts per billion (ppb) (1 ppb is equivalent to 0.001 ppm) or undetectable lead levels in the final product. Consequently, FDA typically finds low parts per billion or undetectable levels of lead in sugar-based candies it analyzes in its monitoring activities. While the manufacture of chocolate does not involve a re-crystallization process, most finished milk chocolate products contain lead levels well below 0.1 ppm.

Many Mexican-style[2] candy products can contain significant amounts of chili powder (hereafter, chili). At the time we issued the 1995 letter, we were aware that candy products with ingredients, such as chili, may contain more lead than sugar-based candies because chili is a minimally refined ingredient which would not be expected to contain lead levels as low as those in highly refined ingredients like sugar.

Since the issuance of the 1995 letter, however, we have found several candy and related products, i.e., "powdered snack mix" products (described below) containing chili to be contaminated with levels of lead that suggest that good manufacturing practices are not being employed in the manufacture of the chili ingredient, resulting in significant contamination of the chili ingredient and finished candy products with lead.

These findings of elevated levels of lead in candy and powdered snack mix products and our belief that such lead contamination is avoidable led FDA to issue a letter to the industry on March 25, 2004 (the 2004 letter) in which FDA announced that it intended to lower the 0.5 ppm guideline for considering enforcement action against candy products containing lead and likely to be consumed frequently by small children.

Concurrent with this document, FDA has issued a guidance document entitled "Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy." This guidance document announces a recommended maximum level for lead in candy likely to be consumed frequently by small children of 0.1 ppm. The guidance states FDAs commitment to take enforcement action against candy containing lead at levels that may pose a health risk. The guidance also rescinds the .5 ppm guideline for considering enforcement action because that level is no longer regarded as consistent with the agency's policy of reducing lead levels in the food supply to reduce consumers' lead exposure to the lowest level that can practically be obtained.

IV. Lead Levels Found in Candy

a. Sugar-Based Candy

As noted above, FDA typically finds undetectable or low parts per billion levels of lead in most sugar-based candies it analyzes. For example, during the period late-1991 through 2002, FDA collected and analyzed 40 samples of suckers (lollipops of various flavors) as components of market baskets in its Total Diet Study (TDS) program.[3] Of the 40 sucker samples analyzed, FDA did not detect lead in 33 samples, and detected lead at levels too low to reliably quantify (referred to as a "trace" levels) in 7 samples. Based on all 40 results, the mean (average) estimated lead level was 4 ppb, with a standard deviation of 9 ppb and a maximum estimated trace value of 38 ppb. For granulated white sugar samples collected in the TDS during the same period, FDA did not detect lead in 39 of 40 samples it analyzed, and found a trace level of 18 ppb in the remaining sample. These results are what we would expect to find in sugar and sugar-based foods, consistent with the current FCC specification for lead in sucrose (sugar) of 0.1 ppm (100 ppb) because food ingredients typically are manufactured to contain average levels of contaminants that are well below the applicable limit to ensure that lots of the ingredient containing lead at the high end of the production range will still be below the applicable limit. Accordingly, FDA believes that sugar-based candy products can be made with lead levels below 0.1 ppm.

b. Chocolate Candy

FDA's TDS data on milk chocolate candy during the period mid-1991 through 2002 indicate that the mean lead level in 40 samples of milk chocolate candy bars was 0.025 ppm, the standard deviation was 0.018 ppm, and the maximum lead level found was 0.110 ppm. Data

provided to FDA by the chocolate industry in 2005 (Ref. 4) indicate that the mean lead level in 137 milk chocolate samples (consisting of 7 products) was 0.028 ppm, the standard deviation was 0.022 ppm, and the maximum lead level found was 0.222 ppm. The industry data showed one additional sample with a lead level slightly greater than 0.1 ppm; all other lead levels in products tested were below 0.1 ppm.

The chocolate industry data indicate that the mean lead level in 226 dark chocolate samples (consisting of 9 products) was 0.048 ppm, the standard deviation was 0.029 ppm, and the maximum lead level found was 0.275 ppm. Several dark chocolate samples had lead levels exceeding 0.1 ppm, and more dark chocolate than milk chocolate samples had lead levels approaching 0.1 ppm. Dark chocolate samples tended to have higher lead levels than milk chocolate samples because chocolate liquor is the principal source of lead in chocolate products, and dark chocolate products contain higher amounts of chocolate liquor than milk chocolate products.

We believe that if milk chocolate manufacturers source their raw materials appropriately, lead levels in their finished products will not exceed 0.1 ppm lead. With respect to dark chocolate, we expect lead levels to be higher than lead levels in milk chocolate due to the higher chocolate liquor content of dark chocolate. However, we believe that the consumption of dark chocolate products by children is limited. Results of the United States Department of Agriculture's (USDA's) 1994-96, 1998 Continuing Survey of Food Intakes by Individuals (CFSII) indicate that less than 1% of the children under age 6 surveyed consumed dark chocolate. We believe that, if dark chocolate manufacturers source their raw materials appropriately, lead levels in their finished products will not exceed 0.1 ppm.

c. Mexican-Style Candy[4]

i. **With Chili as an Ingredient**

As noted above, we have found elevated levels of lead in Mexican-style candy products that contain chili. For example, from October 2000 to February 2004, we analyzed 132 candy products from Mexico, including powdered snack mix products for lead as part of our imported foods monitoring activity (Ref. 5). Fifty-two of these products had no detectable lead, while 51 had detectable levels of lead that did not exceed 0.150 ppm. Eleven products had lead levels in the 0.151-0.250 ppm range while eighteen had lead levels greater than 0.250 ppm. Among the latter group, 10 of the 18 products contained chili, and based upon visual observation, we believe that some contained significant amounts of chili.[5]

When monitoring for lead levels in its TDS, FDA typically finds that fresh peppers contain lead at non-detectable levels or trace levels. During the mid-1991 through 2002 period, FDA analyzed 40 samples of raw green peppers in its TDS and did not detect lead in 37 samples, while it detected trace levels of lead in 3 samples with a maximum estimated level of 14 ppb. Although FDA currently has only limited data on chili peppers, because chili peppers are similar in physical characteristics to green peppers, we believe that freshly grown raw chili peppers are not likely to be inherently contaminated with lead. Industry has, however, reported to FDA that chili can become contaminated with lead when soil deposits (which contain some level of lead) that accumulate on peppers

from their growing and handling in open fields, are not removed by a washing step prior to grinding the dried peppers into chili powder. (Ref. 6). The lead introduced by the deposited soil is further concentrated by the drying of the peppers.[6]

Information reported to FDA by the industry indicates a broad range of lead levels in finished chili available in Mexico, and that higher levels of lead are present in chili from unwashed peppers (Ref. 6). Chili made from washed peppers averaged 0.241 ppm lead (range 0.023 to 1.14 ppm) while chili made from unwashed chili peppers averaged 0.938 ppm lead (range 0.049 to 2.21 ppm). These data suggest that Mexican-style candy manufacturers could significantly reduce lead levels in their candy products by ensuring that their chili ingredients are sourced from suppliers that effectively wash the peppers before they are ground. Consequently, even for high-chili-content candy and powdered snack mix products, we believe that candy with appropriately sourced ingredients will not exceed 0.1 ppm lead.[7]

ii. **Salt-BasedPowdered Snack Products**

Included in the 7 Mexican-style candy products tested by FDA that contained over 0.5 ppm lead were 3 powdered snack mix products that did not contain chili, but contained salt as their primary ingredient. Industry has reported to FDA that Mexican salt-based snack products can contain more than 50% salt (Ref. 6), and FDA has encountered powdered snack mix products consisting of only salt, citric acid and flavoring (the latter two ingredients are refined ingredients that are not likely to contain significant amounts of lead). The finding of elevated levels of lead in such products suggests that salt is a source of lead contamination in some imported powdered snack mix products. Since salt available for use as a food ingredient in Mexico is reported to contain lead ranges of 0.01-0.08 ppm for marine salt and 0.1-1.5 ppm for mined salt (Ref. 6) we believe that salt at the high end of the range for mined salt was used in formulating some powdered snack mix products resulting in the food containing avoidable lead contamination. We believe that if manufacturers source salt to minimize lead levels, finished, high-salt- content powdered snack mix products will not exceed 0.1 ppm lead.

iii. **Tamarind Pulp**

Tamarind pulp is a popular ingredient in many Mexican-style candy products. Industry information submitted to FDA states that tamarind pulp may be present at levels not exceeding 5% in sugar-based Mexican candies. (Ref. 6) Although FDA has encountered some tamarind candy products packed in poorly made lead glazed bowls from which very high levels of lead leached into the candy,[8] the industry information for 22 samples of tamarind pulp from Mexico showed an average lead concentration of 0.014 ppm, with a standard deviation of 0.005 ppm, and a range of 0.006 to 0.028 ppm. These data suggest that tamarind as an ingredient can be produced under good manufacturing practices such that it is not likely to be a significant source of elevated lead levels in Mexican-style candies.

d. Other Candy Ingredients and Other Types of Candy

FDA reviewed data on lead levels in other common candy ingredients and other types of candy.

For example, peanuts are a common candy ingredient. During the period mid-1991 through 2002, FDA collected and analyzed 40 samples of dry roasted peanuts as components of market baskets in its TDS. FDA did not detect lead in 39 of the 40 samples. FDA detected a trace amount of lead, estimated at 17 ppb, in the remaining sample.

Other types of nuts are used as candy ingredients. For mixed nuts collected in the TDS during the period mid-1991 through 2002, FDA did not detect lead in 33 of 40 samples it analyzed. FDA detected trace levels of lead in 6 of the 40 samples with a mean lead level of 4 ppb, and detected 90 ppb lead in the remaining sample.

Raisins are used as candy ingredients. During the period mid-1991 through 2002, FDA collected and analyzed 40 samples of raisins as components of market baskets in its TDS. FDA did not detect lead in 20 of the 40 raisin samples. The other 20 samples contained trace levels, with a mean lead level of 9 ppb, and a maximum estimated value of 31 ppb.

FDA also considered data for caramel candy, a candy typically made from sugar, butter, cream, and sometimes other ingredients such as syrup and flour. During the period mid-1991 through 2002, FDA collected and analyzed 40 samples of caramel candy as components of market baskets in its TDS. FDA did not detect lead in 36 of the 40 caramel candy samples. FDA detected trace levels of lead in the other 4 samples, with a mean lead level of 2 ppb, and a maximum value of 30 ppb.

Having considered data on common candy ingredients and other types of candy (besides sugar-based, chocolate and Mexican-style candy) FDA is not aware of any reason, e.g., ingredient considerations, why other types of candy cannot achieve lead levels of 0.1 ppm or less as we similarly found for sugar-based, chocolate and Mexican-style candies. Accordingly FDA believes that other types of candy besides sugar-based, chocolate and Mexican-style candies can also achieve lead levels of 0.1 ppm or less.

V. Health Protection Considerations

FDA has estimated the potential exposure of small children from the candy products with lead levels no higher than we anticipate to be present in candy produced when we issue the 0.1 ppm guidance level and has concluded that the lead in such candy products would not constitute a health hazard.

We used a modeling technique known as Monte Carlo simulation to estimate the mean and 90th percentile daily intake of lead per small child that would likely result if manufactures produced candy with these anticipated lead levels.[9] We then compared these lead intake levels to FDA's provisional total tolerable intake level (PTTIL) for lead by small children of 6 micrograms per day. (Ref. 1) The simulations incorporated data on lead concentration data from FDA's TDS and from industry, and food consumption data from the 1994-98 CSFII.

The PTTIL is the total daily lead intake from all sources that provides a reasonable margin of protection against the known adverse effects of lead. An estimate of lead intake from a respective type of candy that is low relative to the PTTIL indicates that the candy would not pose a significant risk for adverse health effects from lead exposure.

a. Sugar-Based Candy

For worst case lead levels we would anticipate to occur in sugar-based candy, FDA used the lead distribution data for suckers from the mid-1991 through 2002 TDS. As noted above, the lead distribution data for the 40 samples of suckers had a mean of 4 ppb and a standard deviation of 9 ppb. For consumption of sugar-based candy, FDA based its estimate on the most relevant food codes reported in the 1994-96, 1998 CSFII, i.e., hard candy and butterscotch candy.

The mean and 90th percentile lead intake estimates for sugar-based candy using these inputs were 0.04 and 0.09 micrograms per day for males and females 1-3 years of age, and 0.04 and 0.08 micrograms per day for males and females 4-6 years of age, respectively. (Ref. 7) These lead intake estimates likely represent a worst case scenario because some of the lead data for suckers was obtained during a time period when the FCC specification for lead in sugar was higher than the current value, i.e., 0.5 ppm rather than 0.1 ppm. Because of the lower current specification for lead in sugar, FDA believes that it is possible that the current lead distribution for sugar-based candy may have shifted to lower levels than those used to generate this simulation. Nonetheless, as these lead intake estimates are well below the PTTIL of 6 micrograms per day, FDA believes that sugar-based candies would not pose a significant risk to small children for adverse health effects from lead exposure if sugar-based candies contain the lead levels we would anticipate when we issue the 0.1 ppm guidance level for lead in candy.

b. Chocolate Candy and Other Non-Mexican-Style Candy

For milk chocolate, FDA performed two lead intake calculations using a Monte Carlo simulation. (Ref. 7) One calculation used the lead distribution data for milk chocolate from the 1991-2002 results from the TDS and the other calculation used lead distribution data submitted by the industry. As noted above, the lead distribution data for the 40 TDS samples of milk chocolate had a mean of 25 ppb and a standard deviation of 18 ppb, while the lead distribution data for the 137 industry samples of milk chocolate had a mean of 28 ppb and a standard deviation of 22 ppb. For both milk chocolate calculations FDA used consumption data for milk chocolate from the 1994-96, 1998 CFSII.

The mean and 90th percentile lead intake estimates for milk chocolate using these inputs were 0.25 and 0.52 micrograms per day for males and females 1-3 years of age, respectively, using the TDS data, and 0.29 and 0.60 micrograms per day for males and females 1-3 years of age, respectively, using the industry data. For males and females 4-6 years of age, the mean and 90th percentile lead intake estimates for milk chocolate using these inputs were 0.34 and 0.72 micrograms per day, and 0.38 and 0.82 micrograms per day using the TDS and industry data, respectively.

The lead intake estimates calculated using the TDS and the industry data are consistent, and are well below the PTTIL of 6 micrograms per day. These estimates are based upon data that showed a small portion of milk chocolate samples with lead levels greater than 0.1 ppm. As noted above, FDA believes that, if milk chocolate manufacturers source their raw materials appropriately (which we anticipate will happen when we issue the 0.1 ppm guidance level for lead in candy), their finished products will contain less than 0.1 ppm lead. This would result in slightly lower lead intake levels from milk chocolate than those we estimated. Thus, FDA believes that milk chocolate would not pose a significant risk to small children for adverse

health effects from lead exposure if milk chocolate contains the lead levels we would anticipate when we issue the 0.1 ppm guidance level for lead in candy.

For the intake simulation for dark chocolate (Ref. 7), FDA used the lead distribution data for dark chocolate submitted by the industry. As noted above, the lead distribution data for the 226 industry samples of dark chocolate had a mean of 48 ppb and a standard deviation of 29 ppb. For the dark chocolate lead intake calculation, FDA used consumption data for dark chocolate from the 1994-96, 1998 CFSII.

The mean and 90th percentile lead intake estimates for dark chocolate using these inputs were 0.40 and 0.80 micrograms per day for males and females 1-3 years of age. For males and females 4-6 years of age the mean and 90th percentile lead intake estimates for dark chocolate using these inputs were 0.44 and 0.91 micrograms per day. These lead intake estimates are well below the PTTIL of 6 micrograms per day. These estimates are based upon data that showed some dark chocolate samples with lead levels approaching and above 0.1 ppm. FDA anticipates that any dark chocolate manufacturers who market products likely to be consumed frequently by small children will source their raw materials accordingly and that lead intake levels for children who consume such products would be somewhat lower than those we estimated. FDA believes that dark chocolate products would not pose a significant risk to small children for adverse health effects from lead exposure if the dark chocolate contains the lead levels we would anticipate when we issue the 0.1 ppm guidance level for lead in candy.

FDA believes that lead intakes from other types of candy, excluding Mexican-style candy and powdered snack mix products, would likely be within the range of lead intakes bounded by sugar-based and milk chocolate candies, because common candy ingredients, e.g., peanuts, nuts, and raisins, do not appear to pose the potential to introduce lead into candy products at levels exceeding those in sugar-based and chocolate candy.

c. Mexican-Style Candy and Powdered Snack Mixes

i. **With Chili as an Ingredient**

Both hard sugar-based candies included in the intake estimate above, and soft sugar-based candies containing tamarind pulp are typical of Mexican-style candies that contain chili. For estimating lead intake from these candies, FDA assumed that chili would be present at 15% by weight in both sugar based soft and hard candies, that all the lead in the candy would be contributed by the chili ingredient, that in response to the new guidance Mexican candy manufacturers would source washed chili for their products intended for export to the U.S., and that the chili ingredient contained lead at the levels reported to us for washed chili by the industry, i.e., an average of 0.241 ppm lead (range 0.023 to 1.14 ppm) with a standard deviation of 0.173 ppm. FDA performed a lead intake calculation using a Monte Carlo simulation incorporating these assumptions regarding the chili content of soft and hard candies, and the lead content of chili, using consumption data from the 1994-96, 1998 CFSII for hard candy and for selected soft sugar-based candies (i.e., gum drops and soft fruit candy) that were considered to be suitable surrogates for Mexican-style candies. (Ref. 7)

The mean and 90th percentile lead intake estimates for Mexican-style candy using these

inputs were 0.54 and 1.20 micrograms per day for males and females 1-3 years of age, and 0.60 and 1.31 micrograms per day for males and females 4-6 years of age, respectively. As these lead intake estimates are well below the PTTIL of 6 micrograms per day, FDA believes that Mexican-style candy would not pose a significant risk for adverse health effects from lead exposure if it contains the lead levels we would anticipate when we issue the 0.1 ppm guidance level for lead in candy.

ii. **Salt-Based Powdered Snack Products**

For powdered snack mix products, because the CFSII does not include any foods that are suitable surrogates for powdered snack mix products, FDA estimated lead intake for such products containing sugar, e.g., salt, sugar and chili, and such products not containing sugar, e.g., salt and flavoring or salt and chili, using consumption information for powdered snack mix products obtained from a short-term survey (Ref. 8). We performed a Monte Carlo simulation using the serving size and frequency information from the survey (Ref. 9) and assumed that the worst case lead content of the products would be 0.08 ppm. This level, 0.08 ppm, is the upper end of the reported lead range for marine salt in Mexico (Ref. 6), and salt is the principal ingredient in powdered snack mix products. FDA recognizes that chili can be present at levels up to 30% in powdered snack mix products, and can also be a source of lead in these products. However, FDA believes that manufacturers who use chili in their products are likely to source chili containing less than the average reported lead level for washed chili and are also likely to source salt at the lower end of the reported lead range for marine salt. Therefore, the 0.08 ppm assumption is reasonable for firms that minimize the lead content of their ingredients.

We estimated for children 2-5 years of age, a 90th percentile lead intake for sugar containing powdered snack mix products of about 2.3 micrograms per day, and a 90th percentile lead intake for non-sugar containing powdered snack mix products of about 0.9 micrograms per day. As these lead intake estimates are well below the PTTIL of 6 micrograms per day, FDA believes that Mexican powdered snack mix products would not pose a significant risk for adverse health effects to small children from lead exposure if they contain the lead levels we would anticipate when we issue the 0.1 ppm guidance level for lead in candy.

iii. **With Tamarind as an Ingredient**

As noted above, based upon low concentrations of lead found in tamarind pulp samples, FDA believes that tamarind is not likely to be a significant source of elevated lead levels in Mexican-style candies when the tamarind ingredient or finished candy is produced under good manufacturing practices and not held or packed in lead glazed bowls that may leach elevated levels of lead into the pulp or candy. Because of the low levels of lead found in the sample of tamarind pulp cited above, as opposed to the much higher lead levels that have been reported or found in some chili and salt samples, FDA did not calculate separate lead intake estimates for Mexican-style candy products that contain tamarind, but not chili or salt. We believe that the significant sources of addressable lead exposure from Mexican-style candy products are the chili and salt ingredients in some products.

VI. References

1. Federal Register, Vol. 58, pg. 33860, June 21, 1993.
2. Federal Register, Vol. 44, pg. 51233, August 31, 1979.
3. Bolger, P. Michael, Yess, Norma J., Gunderson, Ellis L., Troxell, Terry C., and Carrington, Clark D., "Identification and reduction of sources of dietary lead in the United States," *Food Additives and Contaminants*, Vol. 13, pg. 53, 1996.
4. "A characterization of lead in chocolate products," provided by the Chocolate Manufactures Association, March 2005.
5. FDA data on analysis of Mexican candy products for lead, October 2000 to February 2004.
6. "A characterization of lead in Mexican candy," Provided by the National Confectioner's Association, March 2005.
7. FDA estimate "Lead intake from candies," prepared 4/21/05.
8. FDA Memorandum, "Analysis of Informal Survey of Consumption of Spicy Mix Products by CLPPB," Michael E. Kashtock, December 13, 2004.
9. FDA Memorandum, "Lead in Spicy Chili Mix Candy," Clark Carrington, April 22, 2005.

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[1] The FCC is a compendium published by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, which contains food-grade specifications for food ingredients; in most cases, these specifications are eventually incorporated into relevant FDA regulations. Since we issued the 1995 letter, the FCC specification for lead in sucrose has been reduced from 0.5 ppm to 0.1 ppm.

[2] "Mexican style" refers to candy which contains ingredients popular in Mexico such as chili and tamarind, which are not typically found in domestic candy in the U.S. We have included within the broad category of Mexican-style candy, powdered snack mix products, which are generally made in Mexico and typically contain combinations of salt, chili powder, sugar and flavoring. These products, popular with children and adults, may be sold alongside of candy in retail outlets, and can be consumed directly from the container like candy, as well as being sprinkled onto fruits and vegetables or in beverages.

[3] The Total Diet Study is a program that has been conducted continuously by the FDA since the 1960s to among other things, monitor levels of chemical contaminants in foods and to estimate the dietary intake of these contaminants. FDA Total Diet Study data cited in this document are available at Total Diet Study: Analytical Results.

[4] We have included within the broad category of Mexican-style candy, powdered snack mix products, which are generally made in Mexico and typically contain combinations of salt, chili powder, sugar and flavoring. These products, popular with children and adults, may be sold

alongside of candy in retail outlets, and can be consumed directly from the container like candy, as well as being sprinkled onto fruits and vegetables or in beverages.

[5] Industry sources have reported to the FDA that sugar-based Mexican-style candy recipes can contain as much as 15% chili, while salt-based products, e.g., some powdered snack mixes, can contain as much as 30% chili (Ref. 6).

[6] USDA's Handbook #8 gives a moisture content for hot chili peppers with seeds of 74%, and when dried (with seeds) of 12%. This equates to a concentration factor of about 6 from drying.

[7] This is based upon the chili content of candy and powdered snack mix products not exceeding 15% and 30% respectively, as has been reported to us by the industry.

[8] The regulatory status of bowls of this type is not addressed in FDA's 2005 guidance on lead levels in candy and powdered snack mix products because it is addressed under FDA's Compliance Policy Guide 7117.07 entitled "Pottery (Ceramics); Imported and Domestic - Lead Contamination."

[9] Monte Carlo simulations (Rubinstein, 1981) can be used to evaluate models in which one or more inputs (in this case, food intakes and lead levels in food) can be defined by a distribution of values. A Monte Carlo simulation takes a random value from the distribution of possible values for the input, uses that value in calculating the outcome of the model, stores the result, and then repeats the procedure a determined number of times (iterations) using new random values of the input taken from the distribution for each iteration. The resulting output from this procedure (e.g., lead intakes) is a range of possible outcomes for the model. A probability distribution function can be prepared from the range and can be used to estimate intakes (typically mean and/or 90th percentile) of substances in the diet.

Guidance for Industry: Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy November 2006

Letter to Manufacturers, Importers, and Distributors of Imported Candy March 25, 2004

Guidance for Industry: Letter to Manufacturers, Importers, and Distributors of Imported Candy and Candy Wrappers June 13, 1995

This document supercedes "Supporting Document for Recommended Maximum Level for Lead in Candy Likely To Be Consumed Frequently by Small Children," December 2005

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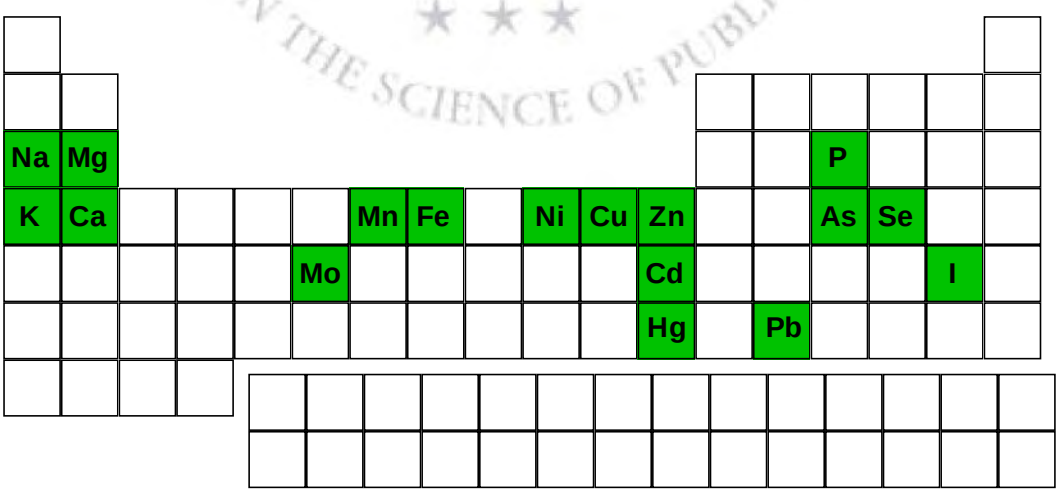
Total Diet Study Statistics on Element Results

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
College Park, MD



Revision 4, Market Baskets 1991-3 through 2004-4
August 21, 2006

Summaries of element analytical results in food and nominal element analytical limits are provided for samples analyzed under the Food and Drug Administration's Total Diet Study program. The information pertains to Total Diet Study market baskets 1991-3 through 2004-4 collected between September 1991 and October 2004.

Notes
• Trace: Analytical result is greater than or equal to the limit of detection but less than the limit of quantification.
• Statistics were calculated using value of 0 for results below the limit of detection.
• Some values have been rounded.

Document Name: Total Diet Study Statistics on Element Results

Revision 4, 1991-2004, August 21, 2006
Revision 3, 1991-2003, August 21, 2005
Revision 2, 1991-2002, July 6, 2004
Revision 1, 1991-1998, April 25, 2000
Revision 0, 1991-1996, June 15, 1999

This document is available on the Internet at <http://www.cfsan.fda.gov/~comm/tds-res.html>.

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Center for Food Safety and Applied Nutrition
Office of Plant and Dairy Foods
Division of Pesticides and Industrial Chemicals
Elemental Research Branch (HFS-338)
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Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Overall:		12,466	9697	2553	0.003	0.009	0	0.210	0
whole milk, fluid	1	48	43	5	0.001	0.003	0	0.011	0
lowfat (2% fat) milk, fluid	2	48	43	5	0.001	0.003	0	0.012	0
chocolate milk, fluid	3	48	42	6	0.001	0.003	0	0.013	0
skim milk, fluid	4	48	42	5	0.001	0.004	0	0.023	0
plain yogurt, lowfat	6	40	36	4	0.001	0.002	0	0.008	0
chocolate milk shake, fast-food	7	48	32	15	0.005	0.008	0	0.023	0
evaporated milk, canned	8	40	38	2	0.001	0.004	0	0.019	0
American, processed cheese	10	48	44	4	0.002	0.006	0	0.024	0
cottage cheese, 4% milkfat	11	40	33	6	0.002	0.006	0	0.030	0
cheddar cheese	12	48	45	3	0.001	0.004	0	0.021	0
ground beef, pan-cooked	13	48	45	2	0.002	0.007	0	0.040	0
beef chuck roast, baked	14	48	43	5	0.002	0.005	0	0.020	0
beef steak, loin, pan-cooked	16	40	36	4	0.002	0.005	0	0.020	0
ham, baked	17	48	44	3	0.002	0.009	0	0.054	0
pork chop, pan-cooked	18	48	44	4	0.001	0.003	0	0.014	0
pork sausage, pan-cooked	19	48	43	5	0.002	0.007	0	0.026	0
pork bacon, pan-cooked	20	48	44	4	0.002	0.006	0	0.027	0
pork roast, baked	21	48	46	2	0.001	0.005	0	0.030	0
lamb chop, pan-cooked	22	48	43	5	0.001	0.004	0	0.020	0
chicken, fried (breast, leg, and thigh) homemade	24	40	38	2	0.001	0.005	0	0.030	0
turkey breast, roasted	26	48	47	1	0	0.002	0	0.014	0
liver, beef, fried	27	48	7	37	0.024	0.018	0	0.080	0.022
frankfurters, beef, boiled	28	48	40	8	0.005	0.011	0	0.043	0
bologna, sliced	29	48	44	4	0.001	0.005	0	0.021	0
salami, sliced	30	48	46	2	0.001	0.003	0	0.016	0
tuna, canned in oil	32	40	36	4	0.001	0.004	0	0.013	0
fish sticks, frozen, heated	34	47	43	4	0.001	0.004	0	0.020	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
eggs, scrambled	35	48	47	1	0	0.001	0	0.009	0
eggs, fried	36	40	39	1	0	0.001	0	0.009	0
eggs, boiled	37	48	46	2	0.001	0.002	0	0.013	0
pinto beans, dry, boiled	38	48	42	6	0.001	0.003	0	0.014	0
pork and beans, canned	39	48	40	8	0.002	0.004	0	0.018	0
lima beans, immature, frozen, boiled	42	48	41	7	0.001	0.004	0	0.020	0
green peas, fresh/frozen, boiled	46	48	40	8	0.002	0.004	0	0.020	0
peanut butter, smooth	47	48	43	5	0.002	0.007	0	0.033	0
peanuts, dry roasted	48	48	47	1	0	0.002	0	0.017	0
white rice, cooked	50	48	43	4	0.001	0.005	0	0.030	0
oatmeal, quick (1-3 min), cooked	51	48	45	3	0.001	0.003	0	0.014	0
wheat cereal, farina, quick (1-3min), cooked	52	48	40	8	0.002	0.005	0	0.022	0
corngrits, regular, cooked	53	48	44	4	0.001	0.005	0	0.024	0
corn, fresh/frozen, boiled	54	48	45	3	0.001	0.003	0	0.014	0
corn, canned	55	8	6	1	0.008	0.019	0	0.055	0
cream style corn, canned	56	40	33	7	0.002	0.005	0	0.020	0
popcorn, popped in oil	57	40	33	7	0.004	0.008	0	0.030	0
white bread	58	48	39	9	0.003	0.006	0	0.024	0
white roll	59	40	27	13	0.006	0.009	0	0.025	0
cornbread, homemade	60	48	35	13	0.004	0.007	0	0.029	0
biscuit, from refrigerated dough, baked	61	48	34	14	0.004	0.006	0	0.018	0
whole wheat bread	62	48	33	15	0.004	0.007	0	0.025	0
tortilla, flour	63	48	41	7	0.002	0.006	0	0.024	0
rye bread	64	48	35	13	0.004	0.008	0	0.030	0
blueberry muffin, commercial	65		41	7	0.002	0.005	0	0.018	0
saltine crackers	66	48	41	7	0.003	0.008	0	0.028	0
corn chips	67	48	47	1	0	0.002	0	0.014	0
pancake from mix	68	40	30	10	0.003	0.006	0	0.020	0
egg noodles, boiled	69	48	29	19	0.004	0.005	0	0.014	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
macaroni, boiled	70	40	34	6	0.001	0.003	0	0.009	0
corn flakes	71	48	42	6	0.002	0.005	0	0.019	0
fruit-flavored, sweetened cereal	72	48	38	9	0.004	0.009	0	0.050	0
shredded wheat cereal	73	48	43	5	0.001	0.005	0	0.026	0
raisin bran cereal	74	48	32	16	0.006	0.009	0	0.036	0
crisped rice cereal	75	48	41	7	0.002	0.006	0	0.030	0
granola cereal	76	48	32	16	0.005	0.008	0	0.026	0
oat ring cereal	77	48	29	19	0.006	0.007	0	0.027	0
apple, red, raw	78	48	38	10	0.002	0.005	0	0.023	0
orange, raw	79	48	43	5	0.001	0.003	0	0.012	0
banana, raw	80	48	43	5	0.001	0.002	0	0.008	0
watermelon, raw	81	48	41	6	0.002	0.006	0	0.040	0
peach, raw	83	48	40	7	0.002	0.006	0	0.030	0
applesauce, bottled	84	48	44	4	0.001	0.002	0	0.009	0
pear, raw	85	48	45	3	0.000	0.002	0	0.008	0
strawberries, raw	86	48	42	6	0.001	0.003	0	0.017	0
fruit cocktail, canned in heavy syrup	87	48	6	34	0.018	0.016	0	0.064	0.013
grapes, red/green, seedless, raw	88	48	32	16	0.003	0.005	0	0.019	0
cantaloupe, raw	89	48	43	5	0.001	0.003	0	0.014	0
plums, raw	91	39	32	7	0.001	0.003	0	0.011	0
grapefruit, raw	92	48	42	6	0.001	0.003	0	0.013	0
pineapple, canned in juice	93	48	9	30	0.010	0.007	0	0.030	0.009
sweet cherries, raw	94	34	28	6	0.002	0.004	0	0.018	0
raisins, dried	95	48	26	22	0.008	0.010	0	0.031	0
prunes, dried	96	40	29	10	0.005	0.010	0	0.040	0
avocado, raw	97	48	46	2	0.001	0.006	0	0.040	0
orange juice, from frozen concentrate	98	48	45	2	0.001	0.003	0	0.020	0
apple juice, bottled	99	48	19	29	0.004	0.004	0	0.018	0.004
grapefruit juice, from frozen concentrate	100	48	48	0	0	0	0	0	0

Lead - Summary of Results

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prune juice, bottled	103	48	31	16	0.003	0.008	0	0.054	0
lemonade, from frozen concentrate	105	48	45	3	0	0.002	0	0.007	0
spinach, fresh/frozen, boiled	107	48	11	33	0.013	0.013	0	0.062	0.010
collards, fresh/frozen, boiled	108	48	13	33	0.012	0.020	0	0.136	0.009
iceberg lettuce, raw	109	48	45	3	0	0.001	0	0.006	0
cabbage, fresh, boiled	110	48	45	3	0	0.002	0	0.008	0
coleslaw with dressing, homemade	111	40	33	7	0.002	0.005	0	0.018	0
sauerkraut, canned	112	40	24	13	0.008	0.014	0	0.069	0
broccoli, fresh/frozen, boiled	113	48	45	3	0.001	0.003	0	0.014	0
celery, raw	114	48	44	4	0.001	0.003	0	0.012	0
asparagus, fresh/frozen, boiled	115	48	40	8	0.002	0.004	0	0.014	0
cauliflower, fresh/frozen, boiled	116	48	44	4	0.001	0.003	0	0.011	0
tomato, red, raw	117	48	46	2	0	0.002	0	0.009	0
tomato sauce, plain, bottled	119	48	34	14	0.004	0.007	0	0.025	0
green beans, fresh/frozen, boiled	121	48	43	4	0.001	0.004	0	0.020	0
beans, snap green, canned	122	8	7	1	0.002	0.004	0	0.012	0
cucumber, raw	123	48	44	3	0.001	0.005	0	0.030	0
summer squash, fresh/frozen, boiled	124	48	42	6	0.001	0.004	0	0.020	0
green pepper, raw	125	48	44	4	0.001	0.003	0	0.014	0
winter squash, fresh/frozen, baked, mashed	126	48	43	5	0.001	0.004	0	0.017	0
onion, mature, raw	128	48	43	5	0.001	0.005	0	0.024	0
beets, canned	131	8	6	2	0.002	0.004	0	0.009	0
radish, raw	132	40	38	2	0.001	0.003	0	0.015	0
French fries, frozen, heated	134	40	39	1	0.001	0.003	0	0.020	0
mashed potatoes, from flakes	135	40	40	0	0	0	0	0	0
white potato, boiled without skin	136	48	47	1	0	0.001	0	0.010	0
white potato, baked with skin	137	48	35	13	0.003	0.006	0	0.020	0
potato chips	138	48	42	6	0.003	0.008	0	0.032	0
scalloped potatoes, homemade	139	40	37	3	0.002	0.008	0	0.034	0

Lead - Summary of Results

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sweet potato, fresh, baked	140	40	10	26	0.014	0.013	0	0.064	0.011
spaghetti with tomato sauce and meatballs, homemade	142	48	43	2	0.002	0.006	0	0.039	0
beef stew with potatoes, carrots, and onion, homemade	143	40	36	4	0.001	0.004	0	0.017	0
chili con carne, beef and beans, canned	145	8	5	3	0.005	0.007	0	0.016	0
macaroni and cheese, from box mix	146	48	44	4	0.001	0.003	0	0.012	0
quarter-pound hamburger on bun, fast-food	147	48	39	8	0.006	0.023	0	0.160	0
meatloaf, homemade	148	48	43	5	0.001	0.004	0	0.016	0
spaghetti with tomato sauce, canned	149	40	33	7	0.002	0.004	0	0.018	0
lasagna with meat, homemade	151	40	34	6	0.002	0.005	0	0.020	0
chicken potpie, frozen, heated	152	48	37	11	0.005	0.009	0	0.031	0
chicken noodle soup, canned, condensed, prepared with water	155	48	35	11	0.005	0.009	0	0.041	0
tomato soup, canned, condensed, prepared with water	156	48	42	6	0.001	0.003	0	0.012	0
vegetable beef soup, canned, condensed, prepared with water	157	48	41	7	0.002	0.005	0	0.021	0
white sauce, homemade	160	40	38	1	0.002	0.008	0	0.050	0
dill cucumber pickles	161	48	10	34	0.019	0.016	0	0.064	0.015
margarine, stick, regular (salted)	162	48	45	3	0.002	0.009	0	0.044	0
butter, regular (salted)	164	48	48	0	0	0	0	0	0
mayonnaise, regular, bottled	166	48	45	2	0.003	0.012	0	0.067	0
half & half cream	167	48	47	1	0	0.003	0	0.022	0
cream substitute, frozen	168	48	38	10	0.003	0.007	0	0.030	0
white sugar, granulated	169	48	47	1	0	0.003	0	0.018	0
pancake syrup	170	48	34	14	0.004	0.007	0	0.019	0
honey	172	48	6	37	0.018	0.011	0	0.040	0.017
tomato catsup	173	48	38	9	0.004	0.009	0	0.040	0

Lead - Summary of Results

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chocolate pudding, from instant mix	175	40	21	19	0.005	0.005	0	0.015	0
vanilla flavored light ice cream	177	48	45	3	0.001	0.002	0	0.011	0
chocolate cake with chocolate icing, commercial	178	48	8	40	0.010	0.006	0	0.026	0.010
yellow cake with white icing, prepared from cake and icing mixes	179	40	29	11	0.003	0.004	0	0.013	0
sweet roll/Danish, commercial	182	48	27	21	0.005	0.007	0	0.024	0
chocolate chip cookies, commercial	183	48	7	41	0.011	0.006	0	0.024	0.012
sandwich cookies with creme filling, commercial	184	48	16	29	0.010	0.009	0	0.040	0.010
apple pie, fresh/frozen, commercial	185	48	31	16	0.006	0.011	0	0.060	0
pumpkin pie, fresh/frozen, commercial	186	48	25	23	0.007	0.008	0	0.027	0
milk chocolate candy bar, plain	187	48	4	39	0.024	0.017	0	0.110	0.021
caramel candy	188	40	36	4	0.002	0.006	0	0.030	0
gelatin dessert, any flavor	190	48	43	4	0.001	0.004	0	0.020	0
cola carbonated beverage	191	48	46	2	0	0.002	0	0.016	0
fruit drink, from powder	193	48	46	2	0	0.001	0	0.005	0
low-calorie cola carbonated beverage	194	48	47	1	0	0.001	0	0.005	0
coffee, decaffeinated, from instant	196	40	36	4	0.001	0.002	0	0.010	0
tea, from tea bag	197	48	42	6	0.001	0.002	0	0.007	0
beer	198	48	48	0	0	0	0	0	0
dry table wine	199	48	2	24	0.018	0.011	0	0.060	0.015
whiskey	200	40	35	4	0.002	0.008	0	0.049	0
tap water	201	34	32	2	0	0.001	0	0.004	0
milk-based infant formula, high iron, ready-to-feed	202	48	47	1	0	0.001	0	0.007	0
milk-based infant formula, low iron, ready-to-feed	203	48	47	1	0	0.001	0	0.005	0
beef, strained/junior	205	48	43	4	0.003	0.013	0	0.090	0

Lead - Summary of Results

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chicken, strained/junior, with/without broth or gravy	207	48	39	9	0.002	0.005	0	0.020	0
chicken/turkey with vegetables, high/lean meat, strained/junior	208	2	1	1	0.006	0.009	0	0.013	0.006
beef with vegetables, high/lean meat, strained/junior	209	2	1	1	0.006	0.008	0	0.012	0
ham with vegetables, high/lean meat, strained/junior	210	2	2	0	0	0	0	0	0
vegetables and beef, strained/junior	211	48	41	7	0.001	0.003	0	0.014	0
vegetables and chicken, strained/junior	212	48	37	10	0.004	0.013	0	0.088	0
vegetables and ham, strained/junior	213	48	40	8	0.002	0.004	0	0.013	0
chicken noodle dinner, strained/junior	214	47	31	16	0.004	0.005	0	0.013	0
macaroni, tomatoes, and beef, strained/junior	215	48	39	9	0.002	0.004	0	0.014	0
turkey and rice, strained/junior	216	48	37	11	0.003	0.006	0	0.020	0
carrots, strained/junior	218	48	24	24	0.005	0.006	0	0.018	0.004
green beans, strained/junior	219	48	39	9	0.002	0.004	0	0.012	0
mixed vegetables, strained/junior	220	48	39	9	0.002	0.004	0	0.014	0
sweet potatoes, strained/junior	221	48	4	32	0.019	0.009	0	0.039	0.020
creamed corn, strained/junior	222	34	31	3	0.001	0.004	0	0.019	0
peas, strained/junior	223	48	46	2	0	0.002	0	0.011	0
creamed spinach, strained/junior	224	40	19	21	0.005	0.006	0	0.020	0.007
applesauce, strained/junior	225	48	41	7	0.001	0.004	0	0.012	0
peaches, strained/junior	226	48	42	6	0.001	0.003	0	0.015	0
pears, strained/junior	227	48	36	12	0.003	0.005	0	0.020	0
apple juice, strained	230	48	35	13	0.002	0.003	0	0.013	0
orange juice, strained	231	48	45	3	0	0.001	0	0.006	0
custard pudding, strained/junior	232	48	46	2	0.001	0.003	0	0.015	0
fruit dessert/pudding, strained/junior	233	48	43	5	0.001	0.003	0	0.010	0
fruit-flavored yogurt, lowfat (fruit mixed in)	235	48	36	11	0.003	0.006	0	0.030	0

Lead - Summary of Results

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Swiss cheese	236	48	41	7	0.002	0.005	0	0.028	0
cream cheese	237	48	42	6	0.002	0.005	0	0.024	0
veal cutlet, pan-cooked	238	40	33	7	0.003	0.006	0	0.025	0
ham luncheon meat, sliced	239	48	44	4	0.002	0.007	0	0.038	0
chicken breast, roasted	240	48	44	4	0.001	0.003	0	0.015	0
chicken nuggets, fast-food	241	48	42	6	0.001	0.004	0	0.016	0
chicken, fried (breast, leg, and thigh), fast-food	242	40	34	6	0.003	0.008	0	0.030	0
haddock, pan-cooked	243	20	16	4	0.003	0.007	0	0.022	0
shrimp, boiled	244	48	19	21	0.021	0.038	0	0.210	0.012
kidney beans, dry, boiled	245	40	36	3	0.001	0.005	0	0.030	0
peas, mature, dry, boiled	246	40	33	7	0.002	0.004	0	0.015	0
mixed nuts, no peanuts, dry roasted	247	40	33	6	0.006	0.017	0	0.090	0
cracked wheat bread	248	48	35	13	0.004	0.007	0	0.024	0
bagel, plain	249	48	40	8	0.003	0.007	0	0.030	0
English muffin, plain, toasted	250	48	31	17	0.005	0.008	0	0.032	0
graham crackers	251	48	19	29	0.010	0.009	0	0.026	0.011
butter-type crackers	252	48	37	11	0.003	0.006	0	0.023	0
apricot, raw	253	34	26	8	0.002	0.004	0	0.014	0
peach, canned in light/medium syrup	254	48	6	32	0.019	0.015	0	0.057	0.017
pear, canned in light syrup	255	48	9	33	0.015	0.013	0	0.067	0.013
pineapple juice, from frozen concentrate	256	48	37	11	0.001	0.003	0	0.010	0
grape juice, from frozen concentrate	257	48	14	32	0.007	0.006	0	0.030	0.006
French fries, fast-food	258	48	40	8	0.003	0.006	0	0.028	0
carrot, fresh, boiled	259	48	36	12	0.003	0.004	0	0.014	0
tomato, stewed, canned	260	40	27	12	0.004	0.007	0	0.028	0
tomato juice, bottled	261	47	38	9	0.002	0.004	0	0.014	0
beets, fresh/frozen, boiled	262	40	30	8	0.004	0.008	0	0.031	0
Brussels sprouts, fresh/frozen, boiled	263	48	40	7	0.003	0.011	0	0.070	0
mushrooms, raw	264	48	43	5	0.001	0.004	0	0.016	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
eggplant, fresh, boiled	265	48	42	4	0.002	0.007	0	0.040	0
turnip, fresh/frozen, boiled	266	48	43	5	0.001	0.003	0	0.012	0
okra, fresh/frozen, boiled	267	48	43	5	0.001	0.003	0	0.018	0
mixed vegetables, frozen, boiled	268	48	41	6	0.003	0.011	0	0.070	0
beef stroganoff, homemade	269	48	35	10	0.004	0.010	0	0.050	0
green peppers stuffed with beef and rice, homemade	270	40	35	4	0.002	0.006	0	0.030	0
chili con carne with beans, homemade	271	40	31	9	0.003	0.006	0	0.019	0
tuna noodle casserole, homemade	272	48	37	11	0.002	0.005	0	0.019	0
Salisbury steak with gravy, potatoes, and vegetable, frozen meal, heated	273	40	33	7	0.002	0.004	0	0.012	0
turkey with gravy, dressing, potatoes, and vegetable, frozen meal, heated	274	40	32	7	0.003	0.006	0	0.030	0
quarter-pound cheeseburger on bun, fast-food	275	48	43	4	0.004	0.016	0	0.106	0
fish sandwich on bun, fast-food	276	47	39	8	0.003	0.007	0	0.030	0
frankfurter on bun, fast-food	277	40	26	13	0.006	0.009	0	0.040	0
egg, cheese, and ham on English muffin, fast-food	278	48	43	4	0.002	0.009	0	0.050	0
taco/tostada, from Mexican carry-out	279	48	39	9	0.002	0.005	0	0.020	0
cheese pizza, regular crust, from pizza carry-out	280	40	33	7	0.002	0.005	0	0.020	0
cheese and pepperoni pizza, regular crust, from pizza carry-out	281	48	41	7	0.002	0.004	0	0.015	0
beef chow mein, from Chinese carry-out	282	40	30	10	0.003	0.005	0	0.018	0
bean with bacon/pork soup, canned, condensed, prepared with water	283	48	41	7	0.001	0.004	0	0.011	0
mushroom soup, canned, condensed, prepared with whole milk	284	40	34	6	0.002	0.004	0	0.016	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
clam chowder, New England, canned, condensed, prepared with whole milk	285	48	15	33	0.009	0.007	0	0.026	0.009
vanilla ice cream	286	48	46	2	0	0.002	0	0.010	0
fruit flavor sherbet	287	48	36	10	0.003	0.005	0	0.023	0
popsicle, any flavor	288	48	39	8	0.004	0.012	0	0.082	0
chocolate snack cake with chocolate icing	289	40	1	38	0.015	0.005	0	0.025	0.015
cake doughnuts with icing, any flavor, from doughnut store	290	48	29	19	0.004	0.005	0	0.017	0
brownies, commercial	291	48	9	36	0.011	0.008	0	0.032	0.011
sugar cookies, commercial	292	48	36	12	0.003	0.005	0	0.017	0
suckers, any flavor	293	48	41	6	0.003	0.008	0	0.038	0
pretzels, hard, salted, any shape	294	48	39	9	0.005	0.010	0	0.030	0
chocolate syrup dessert topping	295	48	5	35	0.018	0.009	0	0.041	0.018
jelly, any flavor	296	48	30	17	0.004	0.007	0	0.026	0
sweet cucumber pickles	297	40	2	18	0.033	0.027	0	0.131	0.023
yellow mustard	298	48	25	19	0.007	0.009	0	0.030	0
black olives	299	48	26	22	0.005	0.007	0	0.029	0
sour cream	300	48	46	1	0.001	0.006	0	0.040	0
brown gravy, homemade	301	40	35	5	0.002	0.005	0	0.020	0
French salad dressing, regular	302	40	37	3	0.003	0.011	0	0.057	0
Italian salad dressing, low-calorie	303	40	32	6	0.007	0.020	0	0.108	0
olive/safflower oil	304	40	40	0	0	0	0	0	0
coffee, from ground	305	48	42	6	0.001	0.002	0	0.010	0
fruit-flavored carbonated beverage	306	48	46	1	0	0.002	0	0.010	0
fruit drink, canned	307	48	43	5	0.001	0.002	0	0.012	0
martini	308	30	28	2	0.001	0.004	0	0.017	0
soy-based infant formula, ready-to-feed	309	48	45	3	0	0.002	0	0.008	0
egg yolk, strained/junior	310	12	10	2	0.002	0.006	0	0.018	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
rice infant cereal, instant, prepared with whole milk	311	39	34	5	0.002	0.005	0	0.021	0
rice cereal, strained/junior	312	20	15	5	0.003	0.005	0	0.016	0
bananas with tapioca, strained/junior	313	48	47	1	0	0.002	0	0.011	0
beets, strained/junior	314	15	11	4	0.002	0.004	0	0.009	0
split peas with vegetables and ham/bacon, strained/junior	316	27	24	2	0.003	0.010	0	0.050	0
teething biscuits	317	48	11	37	0.013	0.008	0	0.030	0.014
salmon, steaks or filets, fresh or frozen, baked	318	28	27	1	0	0.002	0	0.012	0
rice cereal with apple, strained/junior	319	18	11	7	0.004	0.005	0	0.015	0
squash, strained/junior	320	48	43	5	0.001	0.004	0	0.020	0
BF, cereal, oatmeal, dry, prep w/ water	323	8	7	1	0.002	0.004	0	0.012	0
BF, cereal, rice, dry, prep w/ water	324	8	5	2	0.009	0.015	0	0.040	0
BF, cereal, rice w/apples, dry, prep w/ water	325	8	7	1	0.002	0.006	0	0.016	0
BF, veal and broth/gravy	326	8	8	0	0	0	0	0	0
BF, lamb and broth/gravy	327	8	8	0	0	0	0	0	0
BF, turkey and broth/gravy	328	8	8	0	0	0	0	0	0
Meal replacement, liquid RTD, any flavor	331	8	6	2	0.001	0.003	0	0.006	0
Cottage cheese, creamed, lowfat (2% milk fat)	332	8	7	1	0.001	0.002	0	0.007	0
Sour cream dip, any flavor	333	8	6	1	0.010	0.025	0	0.071	0
Beef steak, loin/sirloin, broiled	334	8	7	1	0.001	0.004	0	0.011	0
Luncheon meat (chicken/turkey)	335	8	8	0	0	0	0	0	0
Chicken breast, fried, fast-food (w/ skin)	336	8	8	0	0	0	0	0	0
Chicken thigh, oven-roasted (skin removed)	337	8	8	0	0	0	0	0	0
Chicken leg, fried, fast-food (w/ skin)	338	8	8	0	0	0	0	0	0
Catfish, pan-cooked w/ oil	339	8	6	2	0.003	0.005	0	0.012	0
Tuna, canned in water, drained	340	8	7	1	0.002	0.005	0	0.013	0
Refried beans, canned	341	8	7	1	0.002	0.005	0	0.013	0
White beans, dry, boiled	342	8	7	1	0.001	0.003	0	0.009	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Sunflower seeds (shelled), roasted, salted	343	8	7	1	0.002	0.006	0	0.016	0
Pancakes, frozen, heated	344	8	7	1	0.002	0.005	0	0.014	0
Breakfast tart/toaster pastry	345	8	5	1	0.011	0.016	0	0.037	0
Macaroni salad, from grocery/deli	346	8	7	1	0.002	0.005	0	0.015	0
Spaghetti, enriched, boiled	347	8	7	1	0.002	0.005	0	0.013	0
Apricots, canned in heavy/light syrup	348	8	1	7	0.011	0.006	0	0.018	0.012
Fruit juice blend (100% juice), canned/bottled	350	8	4	4	0.005	0.005	0	0.014	0.003
Cranberry juice cocktail, canned/bottled	351	8	6	2	0.001	0.002	0	0.005	0
Orange juice, bottled/carton	352	8	7	1	0.001	0.002	0	0.005	0
Potato salad, mayonnaise-type, from grocery/de	353	8	8	0	0	0	0	0	0
Potato, mashed, prepared from fresh	354	8	7	1	0.001	0.003	0	0.008	0
Coleslaw, mayonnaise-type, from grocery/deli	355	8	6	1	0.007	0.017	0	0.048	0
Carrot, baby, raw	356	8	5	2	0.008	0.013	0	0.033	0
Lettuce, leaf, raw	357	8	2	6	0.009	0.006	0	0.018	0.011
Sweet potatoes, canned	358	8	2	4	0.016	0.013	0	0.032	0.016
Tomato salsa, bottled	359	8	5	3	0.004	0.005	0	0.011	0
Beef and vegetable stew, canned	360	8	8	0	0	0	0	0	0
Lasagna w/ meat, frozen, heated	361	8	7	1	0.002	0.004	0	0.012	0
Beef w/ vegetables in sauce, from Chinese carry	362	8	6	2	0.003	0.005	0	0.012	0
Chicken w/ vegetables in sauce, from Chinese c	363	8	7	1	0.001	0.004	0	0.010	0
Fried rice, meatless, from Chinese carry-out	364	8	7	1	0.002	0.004	0	0.012	0
Burrito w/ beef, beans and cheese, from Mexica	365	8	6	2	0.004	0.008	0	0.019	0
Chicken filet (broiled) sandwich on bun, fast-fo	366	8	6	1	0.013	0.032	0	0.090	0
Soup, Oriental noodles (ramen noodles), prep w	367	8	6	2	0.004	0.007	0	0.020	0
Pudding, ready-to-eat, flavor other than chocola	368	8	7	1	0.001	0.002	0	0.007	0
Cake, yellow w/ icing	369	8	3	4	0.013	0.015	0	0.044	0.012
Granola bar, w/ raisins	370	8	6	2	0.003	0.006	0	0.014	0
Candy bar, chocolate, nougat, and nuts	371	8	4	4	0.010	0.012	0	0.031	0.007
Popcorn, microwave, butter-flavored	372	8	6	2	0.004	0.008	0	0.018	0

Lead - Summary of Results

TDS Food Description	TDS Food No.	Number of Results	Number Not Detected	Number of Traces	Mean (mg/kg)	Standard Deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Sweet & sour sauce	373	8	6	2	0.004	0.008	0	0.021	0
Brown gravy, canned or bottled	374	8	7	1	0.002	0.005	0	0.014	0
Salad dressing, creamy/buttermilk type, regular	375	8	6	1	0.012	0.027	0	0.077	0
Salad dressing, creamy/buttermilk type, low-cal	376	8	2	5	0.015	0.012	0	0.040	0.015
Salad dressing, Italian, regular	377	8	5	3	0.009	0.013	0	0.032	0
Olive oil	378	8	8	0	0	0	0	0	0
Vegetable oil	379	8	7	1	0.003	0.007	0	0.021	0
Bottled drinking water (mineral/spring), not carl	380	8	7	1	0.001	0.002	0	0.005	0
Decaffeinated coffee, from ground	381	8	6	2	0.002	0.005	0	0.013	0
Decaffeinated tea, from tea bag	382	8	8	0	0	0	0	0	0

Lead Exposure: Sources & Effects

Susan K. Cummins, MD, MPH
Medical Team Leader
Division of Pediatric Drug Development

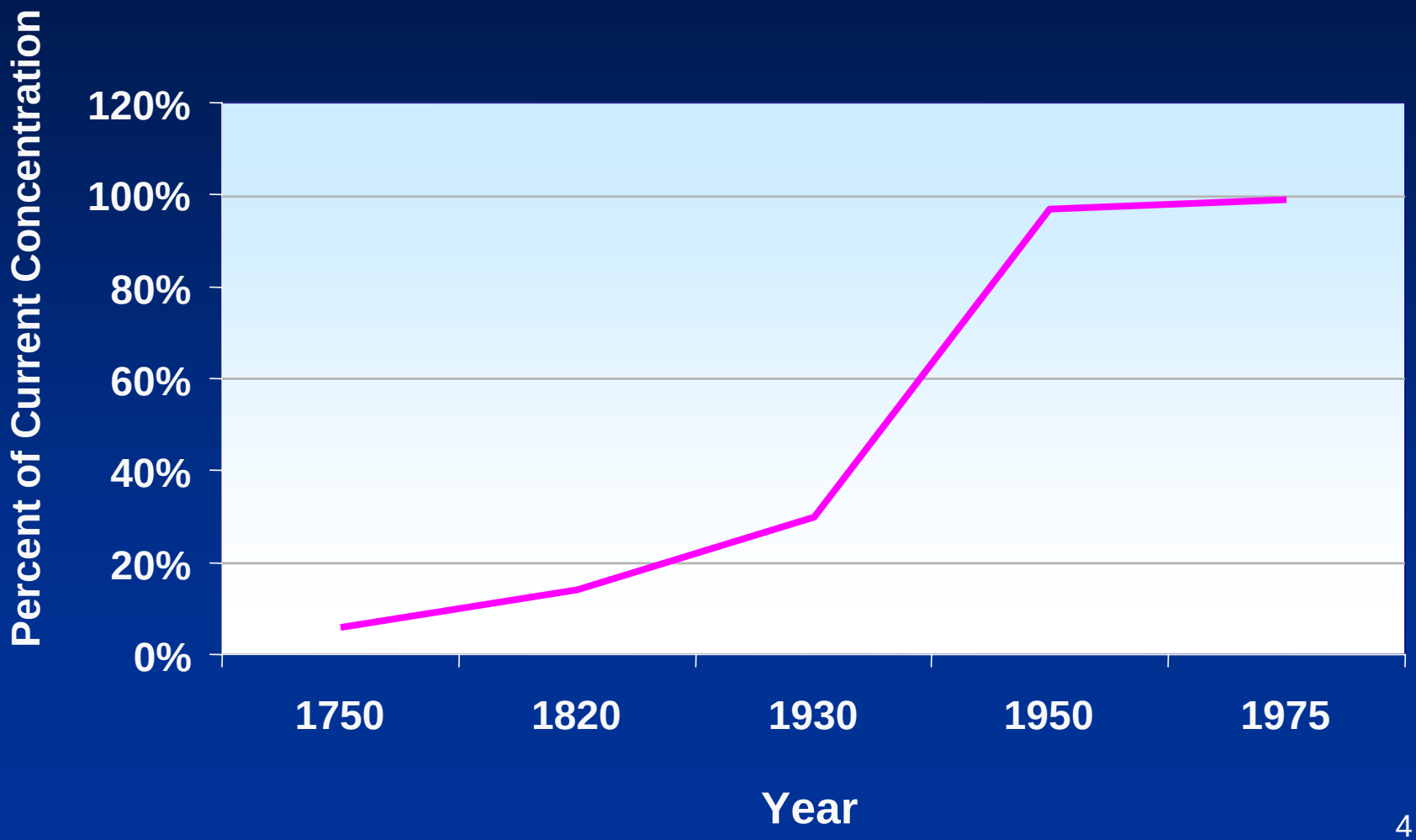
Today's Talk

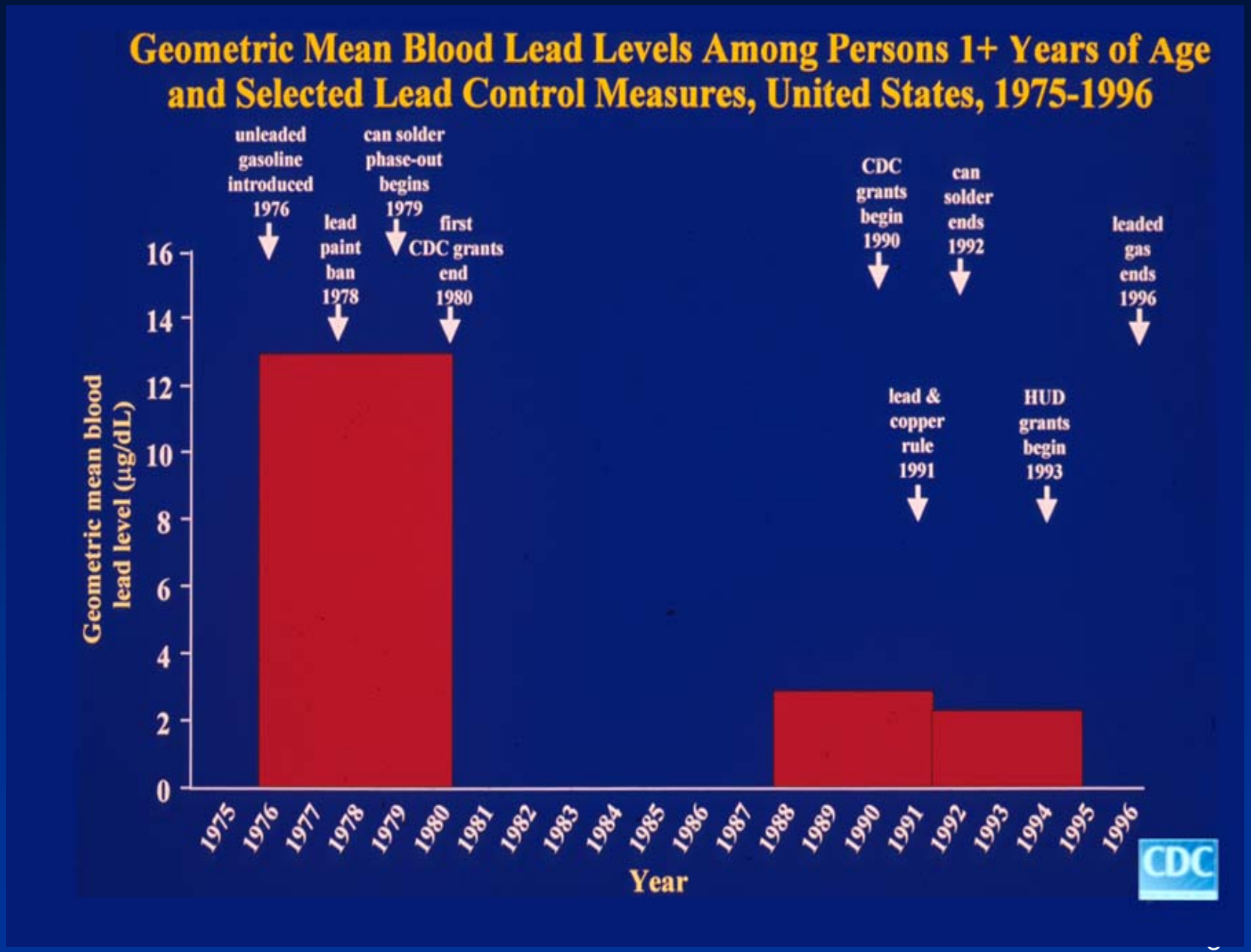
- Exposure Sources and Pathways
- Blood Lead Level Trends for Children, Pregnant Women and Adults
- Health Effects in Children and Adults
- Regulatory Standards

Key Take-Away Lessons

- Lead is a systemic toxicant
- Multiple sources of exposure exist
- There is no safe exposure threshold
- Public health efforts to reduce lead exposure have worked
- The elderly have higher lead burdens than the young

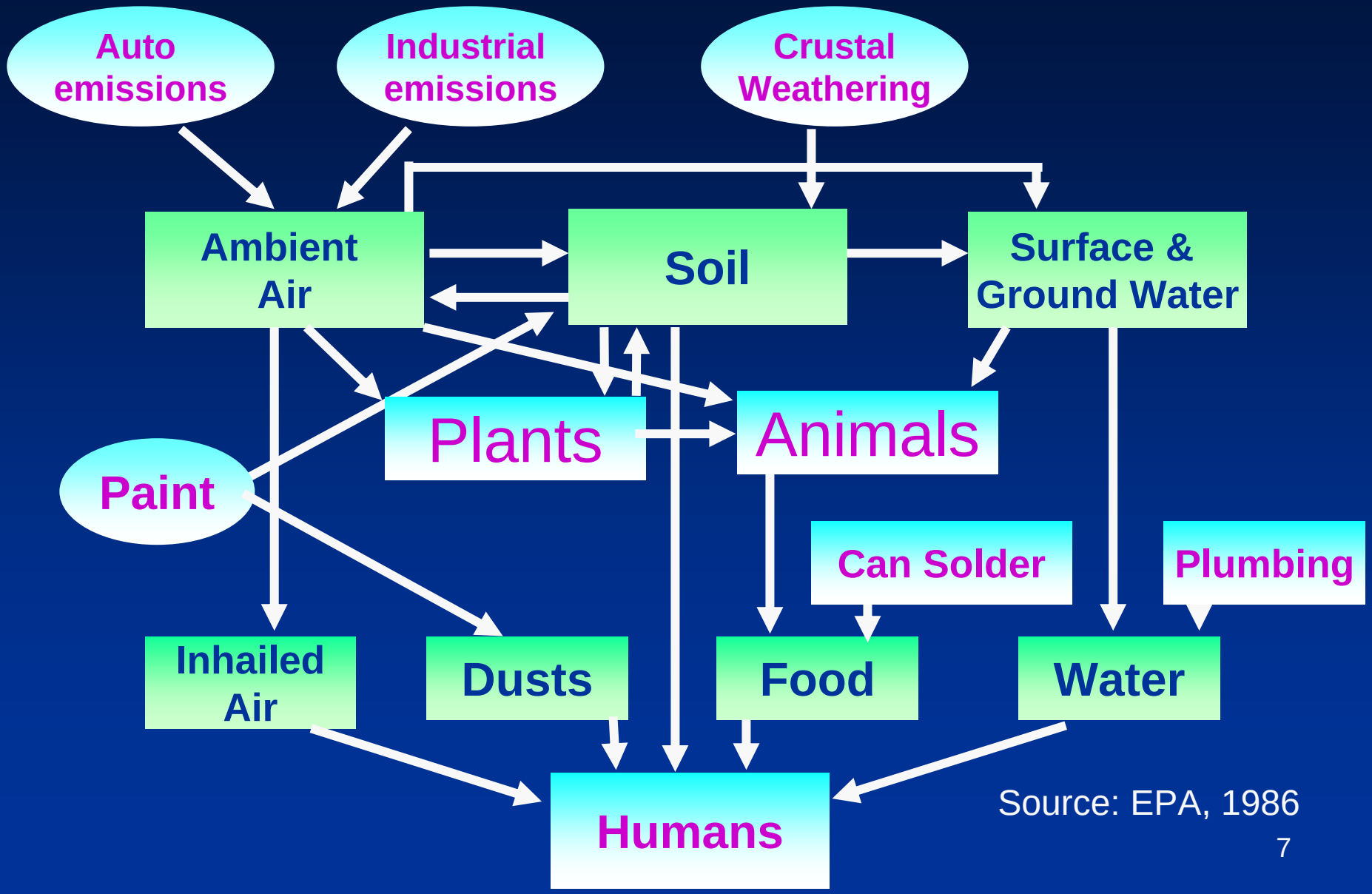
Lead in Arctic Snow Strata




Geometric Mean Blood Lead Levels Among Persons 1+ Years of Age and Selected Lead Control Measures, United States, 1975-1996
unleaded gasoline introduced 1976
lead paint ban 1978
can solder phase-out begins 1979
first CDC grants end 1980
CDC grants begin 1990
can solder ends 1992
leaded gas ends 1996
lead & copper rule 1991
HUD grants begin 1993
Geometric mean blood lead level (µg/dL)
0
2
4
6
8
10
12
14
16
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
Year
CDC

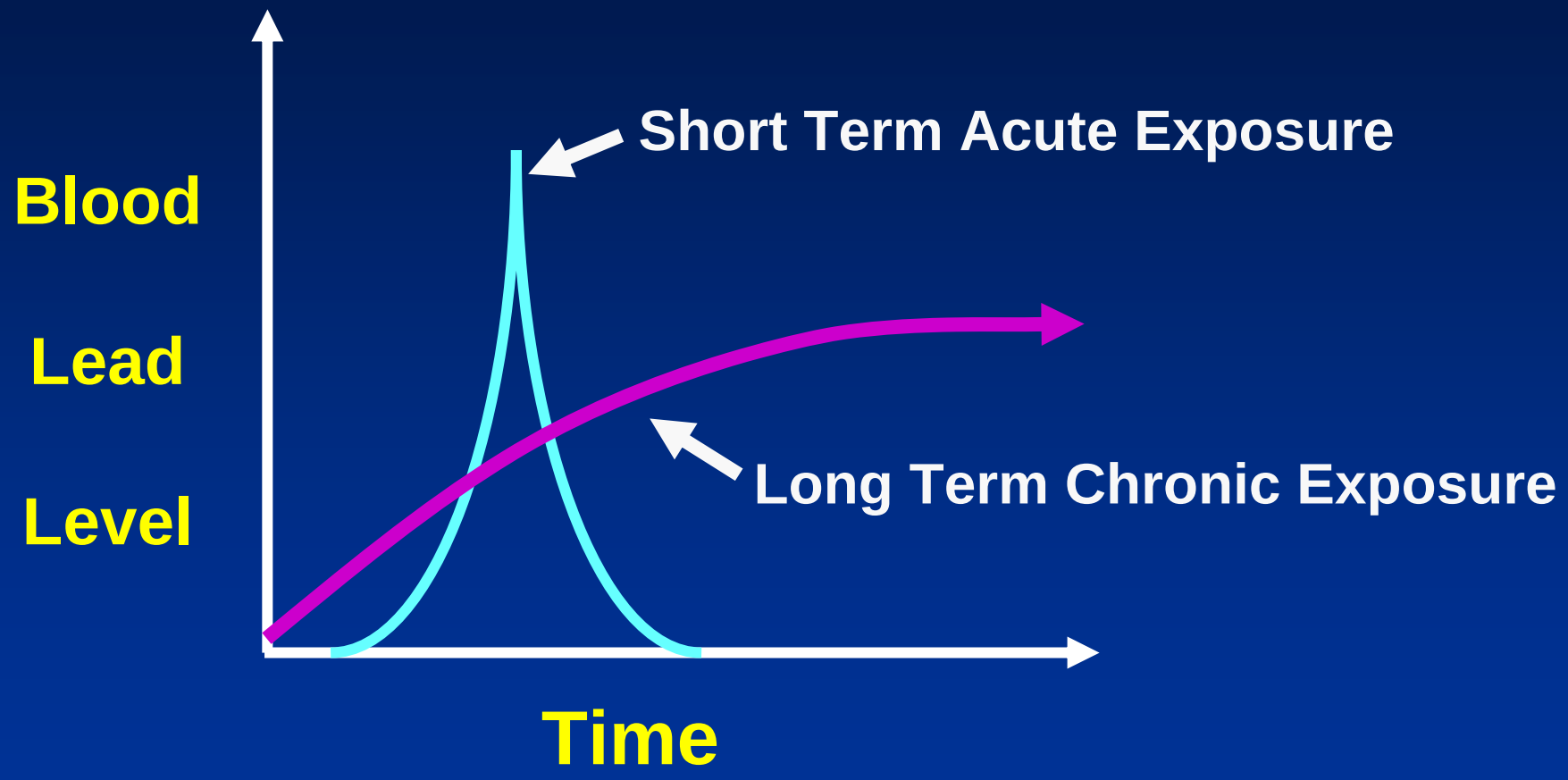
Exposure Sources & Pathways

Lead Exposure Sources & Pathways



Source: EPA, 1986

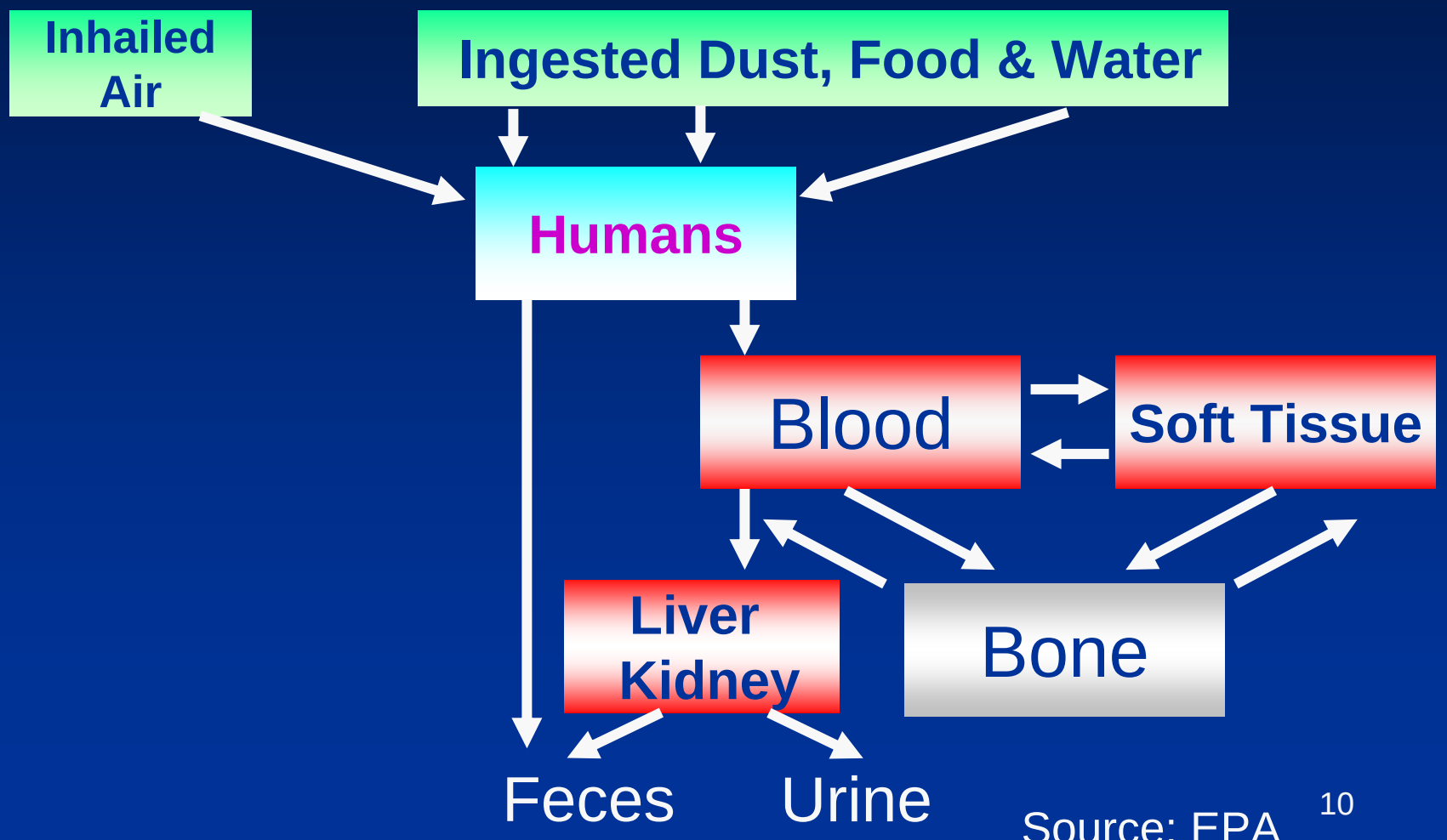
Exposure Scenarios



Lead Metabolism

- Absorption of inhaled or ingested lead
  - Children -- 50%
  - Adults -- 15%
- Most lead is stored in the bones with a half-life of approximately 10 to 15 years

Lead Adsorption, Deposition & Excretion



Source: EPA

Common Lead Sources for Children

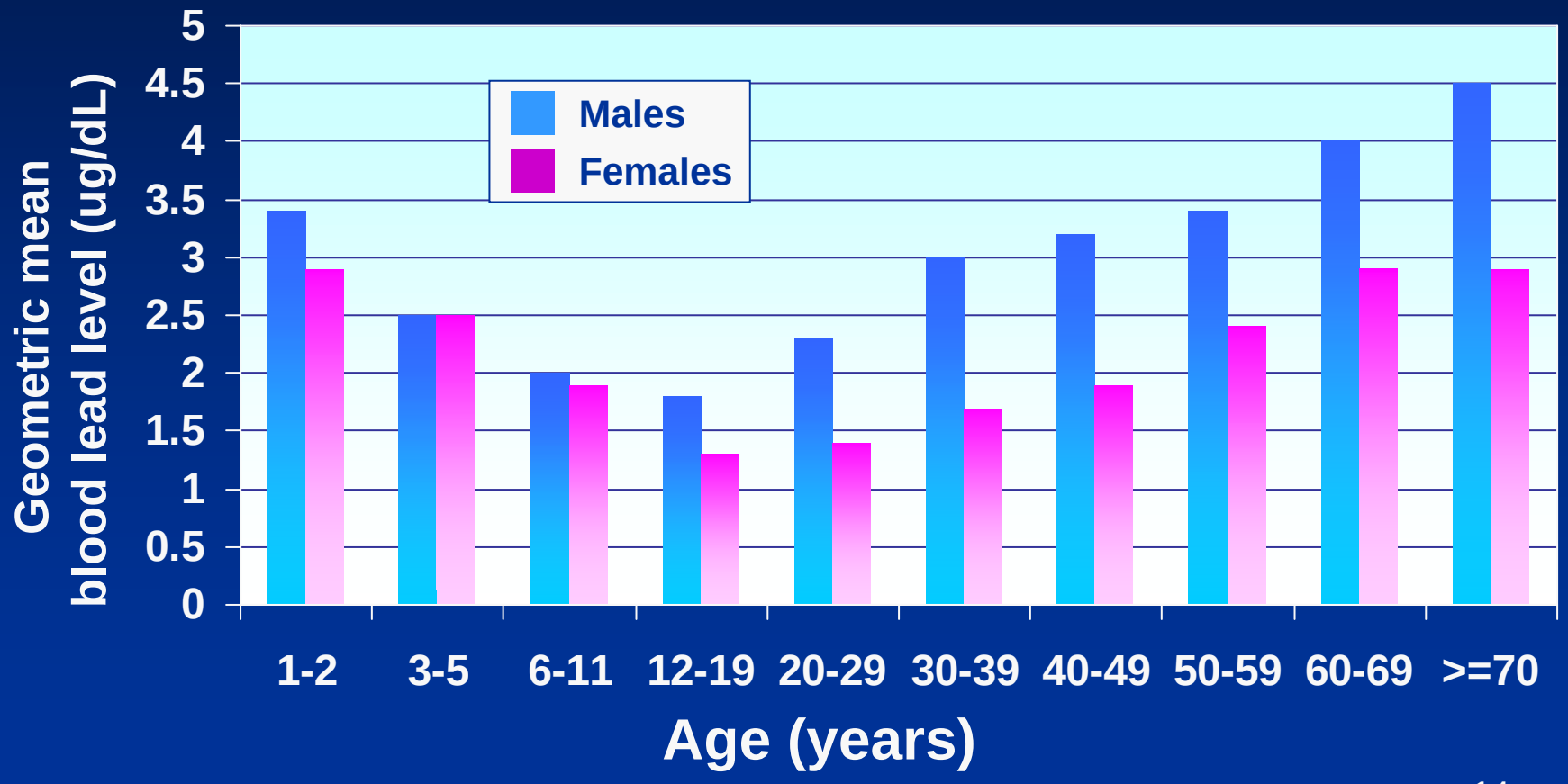
- Deteriorated leaded paint, dust
- Lead contaminated soil
- Lead-contaminated drinking water
- Occupational take-home exposure
- Ethnic remedies (pay-loo-ah, azarcon & greta)
- Food & food containers (tamarind candy, lead glazed ceramics)
- Imported cosmetics (kohl, surma)
- Other (fishing sinkers, lead shot)

Common Lead Sources for Adults

- Occupational exposure -- 90%
  - Construction trades
  - Battery and metal recycling
  - Radiator repair
  - Vinyl plastic manufacture
- Hobbies (packing shot, stained glass)
- Folk remedies & cosmetics (azarcon, greta, kohl, surma, others)

Blood Lead Level Trends for Children, Pregnant Women and Adults

Geometric Mean Blood Lead Levels by Gender & Age NHANES III, 1991 to 1994



Env Health Perspect, 1998

Blood Lead Levels Among Pregnant Women

- Few pregnant women have blood lead screening
- Hospital-based survey of 1,892 women recruited post-partum
  - 1995 to 1998
  - King-Drew Medical Center, South-Central Los Angeles (mostly Latino women)
  - Geometric mean BLL was 2.2 ug/dL
  - Immigrant blood lead > non-immigrant
  - Pica of lead-glazed pottery caused large increase in blood lead

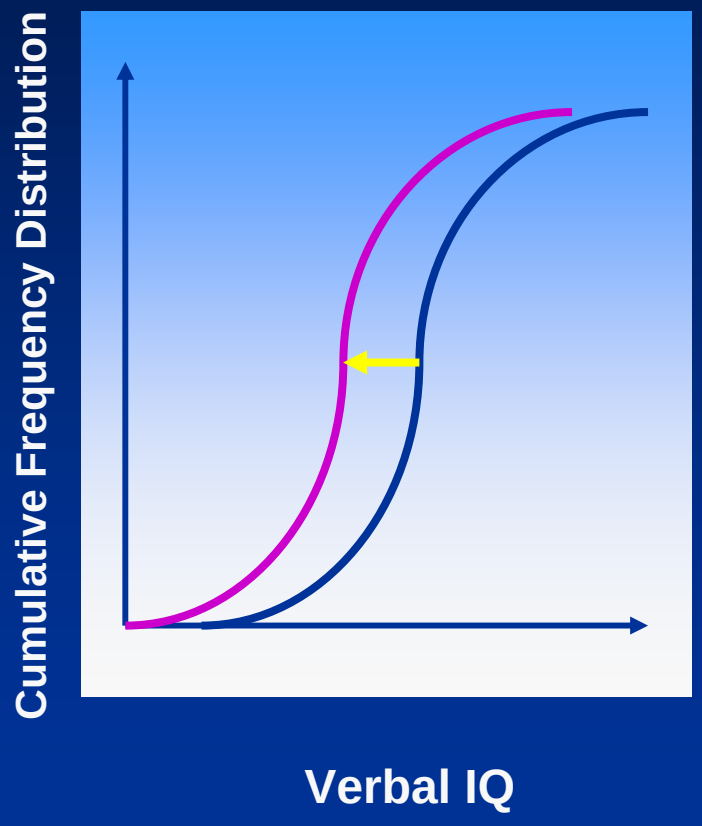
Arch Env Health, 1999

Health Effects in Children & Adults

Lead is a Systemic Toxicant
Health Effects in Children

CDC Level of Concern	Lead in Blood (ug/dL)	Adverse Effect
	150	Death
	100	Acute Encephalopathy
	80	
	70	
	60	Abdominal pain Microcytic anemia
1978	30	
1985	25	Attention Deficits Learning Disabilities School Failure Behavior Problems Reduced IQ
1991	10	
	5	

Blood Lead & IQ



- Blood lead ≥ 10 ug/dL lowers IQ by 2 to 4 points
  - **Doubles low IQ**
  - **Halves high IQ**
- Blood lead 1 to 10 ug/dL lowers IQ by 7 points

Health Effects in Adult Workers

- Hematological: Microcytic anemia from inhibition of heme synthesis (BLL $\geq$ 40 ug/dL)
- Neurological:
  - Irritability, insomnia, fatigue, headache, poor memory, tremor, depression
  - Acute encephalopathy
  - Peripheral neuropathy (motor > sensory, extensor muscles),
    slowing of nerve conduction (BLL $\geq$ 50 ug/dL)

Health Effects in Adult Workers

- Gastrointestinal: colic, constipation anorexia, nausea, vomiting (BLL $\geq$ 80 ug/dL)
- Renal toxicity:
  - Gradual impairment of renal function leading to interstitial fibrosis
  - Hypertension, hyperuricemia with/without gout
- Reproductive effects:
  - Males—impotence, malformed sperm with reduced motility, hypospermia
  - Women—menstrual disturbances, sterility, spontaneous abortions, stillbirths
  - Both--genetic damage to germ cells

Health Effects in Adults From Low Level Exposure

- Data sets:
  - Nurses' Health Study
  - National Health and Nutrition Survey
  - Normative Aging Study

Methods—Lead Effect Studies within the Normative Aging Study

- Cohort of 2,280 Boston resident men
- Enrollment began 1961
- 21 to 80 years old at enrollment
- Few employed in lead occupations
- No chronic diseases or HTN at entry
- Follow up every 3 to 5 years (survey, physical exam, laboratory work)
- Selected subset of 719 men without occupational exposure at entry

Lead Burden Assessment Normative Aging Study

- 1991: Blood lead & bone lead measured
- Blood Lead Distribution (n and percent):
  - Below 5 ug/dL (270) 38%
  - 5 to 10 ug/dL (361) 50%
  - 11 to 20 ug/dL (80) 11%
  - ≥ 20 ug/d (8) 8%
- Bone Lead Burden (range and geometric mean):
  - Tibia: (<1-51 ug/g bone) & 20.8 ug/g bone
  - Patella: (3-77 ug/g) & 29.8 ug/g bone
- Bone lead level correlated with & was the major contributor to blood lead level

Renal Function, Hypertension, & Cognitive Function in the Normative Aging Lead Study

After covariate adjustment:

- Renal function: 10X increase in BLL predicted 0.08 ug/dL increase in serum creatinine
- Hypertension: Odds Ratio of 1.5 for bone lead increase from midpoint of the lowest quintile to mid-point of the highest quintile
- Cognitive Function: higher BLLs and bone lead concentrations correlated with poorer performance on several measures of cognitive performance

JAMA, 1996 and Neurotoxicol Teratol 1997

Which Agency regulates Lead?

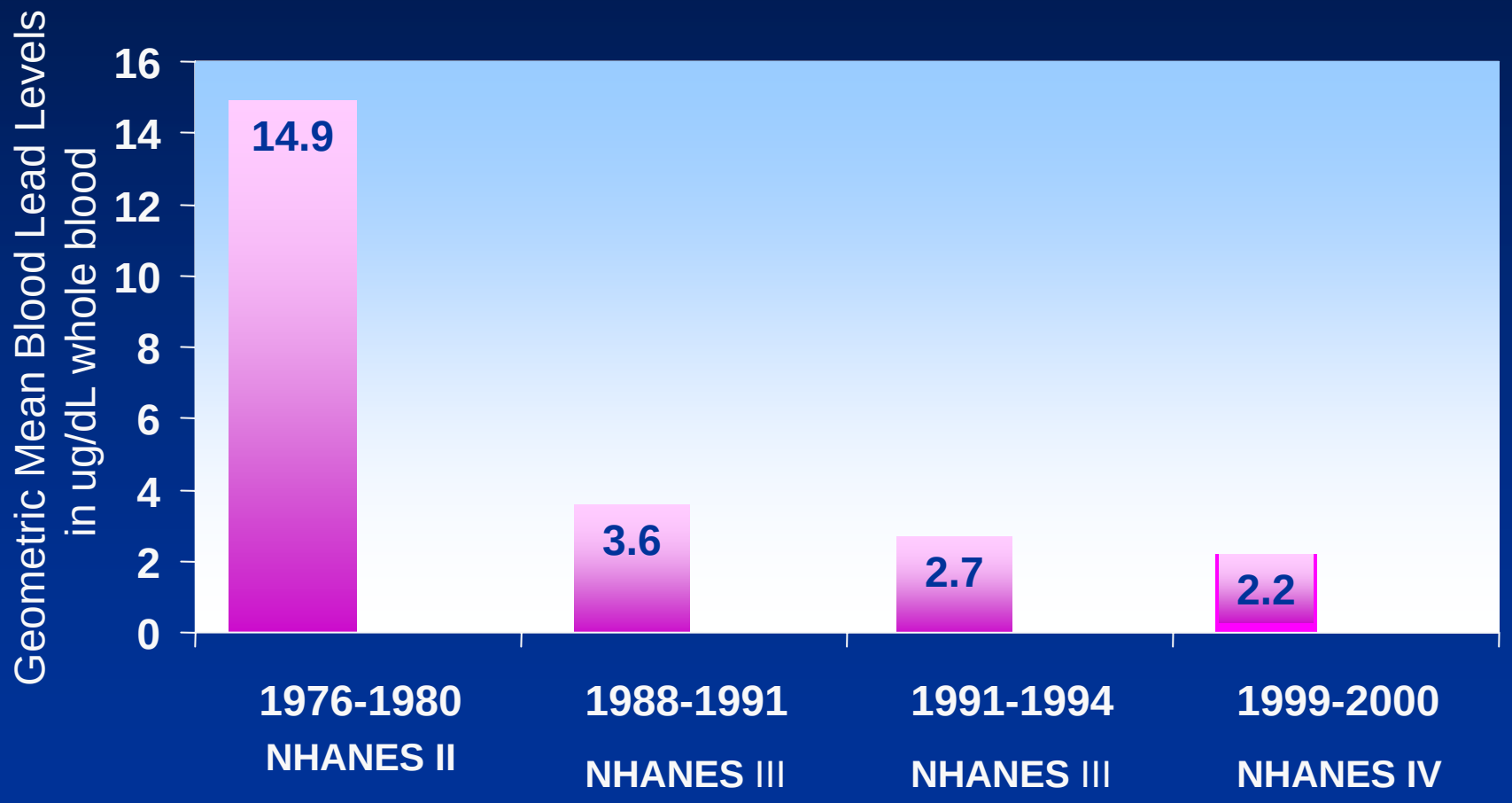
- CPSC--New Paint and consumer products (candle wicks, jewelry, vinyl mini-blinds)
- HUD & EPA--Lead-based paint, dust, residential soil
- EPA--Air, water, plumbing, gasoline
- OSHA--Occupational sources
- FDA--Food containers, food, cosmetics

Key Take-Away Lessons

- Lead is a systemic toxicant
- Multiple sources of exposure exist
- There is no safe exposure threshold
- Public health efforts to reduce lead exposure have worked
- The elderly have higher lead burdens than the young

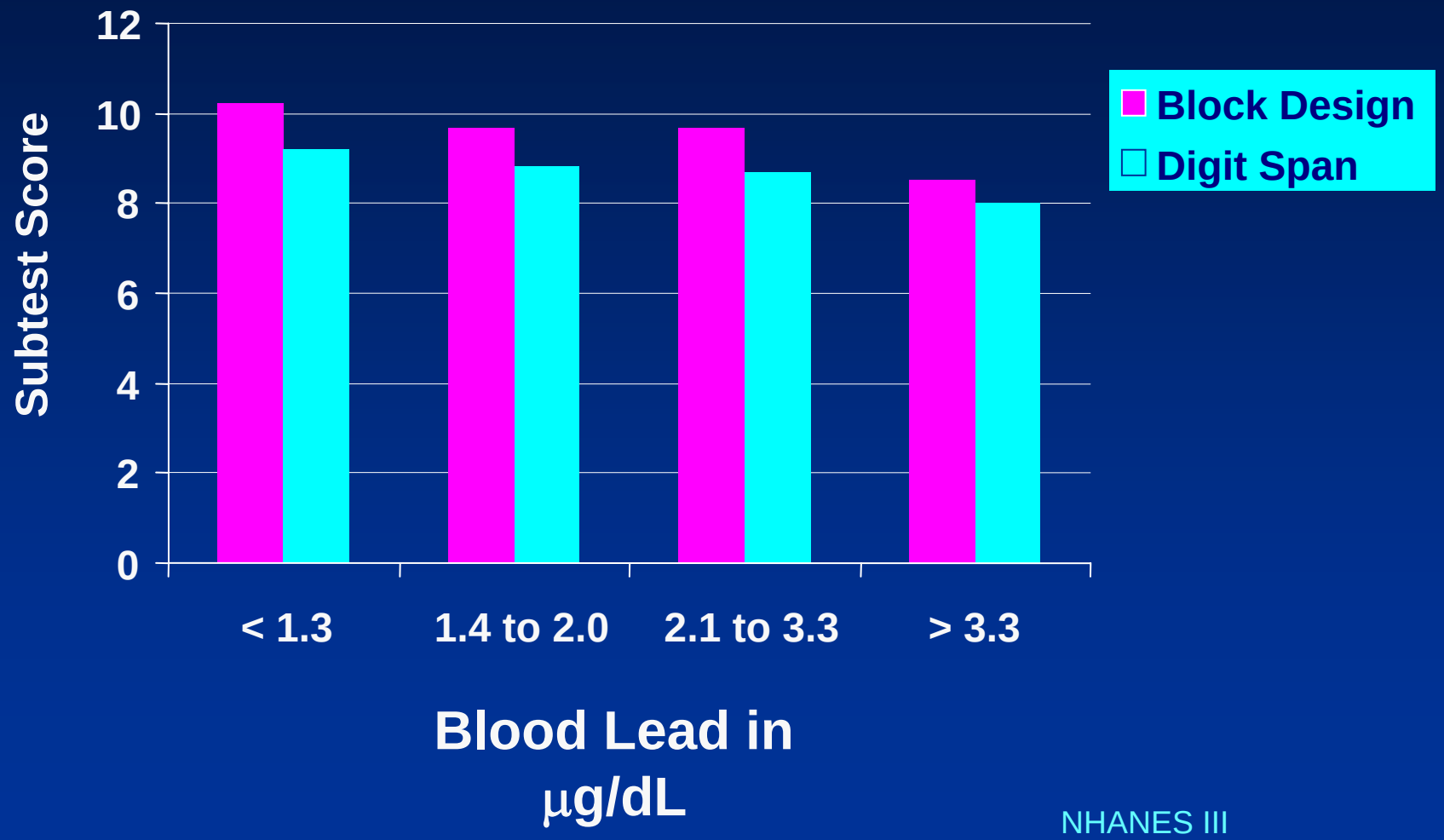
Backup Slides

Geometric Mean Blood Lead Levels in Children 1 to 5 years National Health & Nutrition Surveys



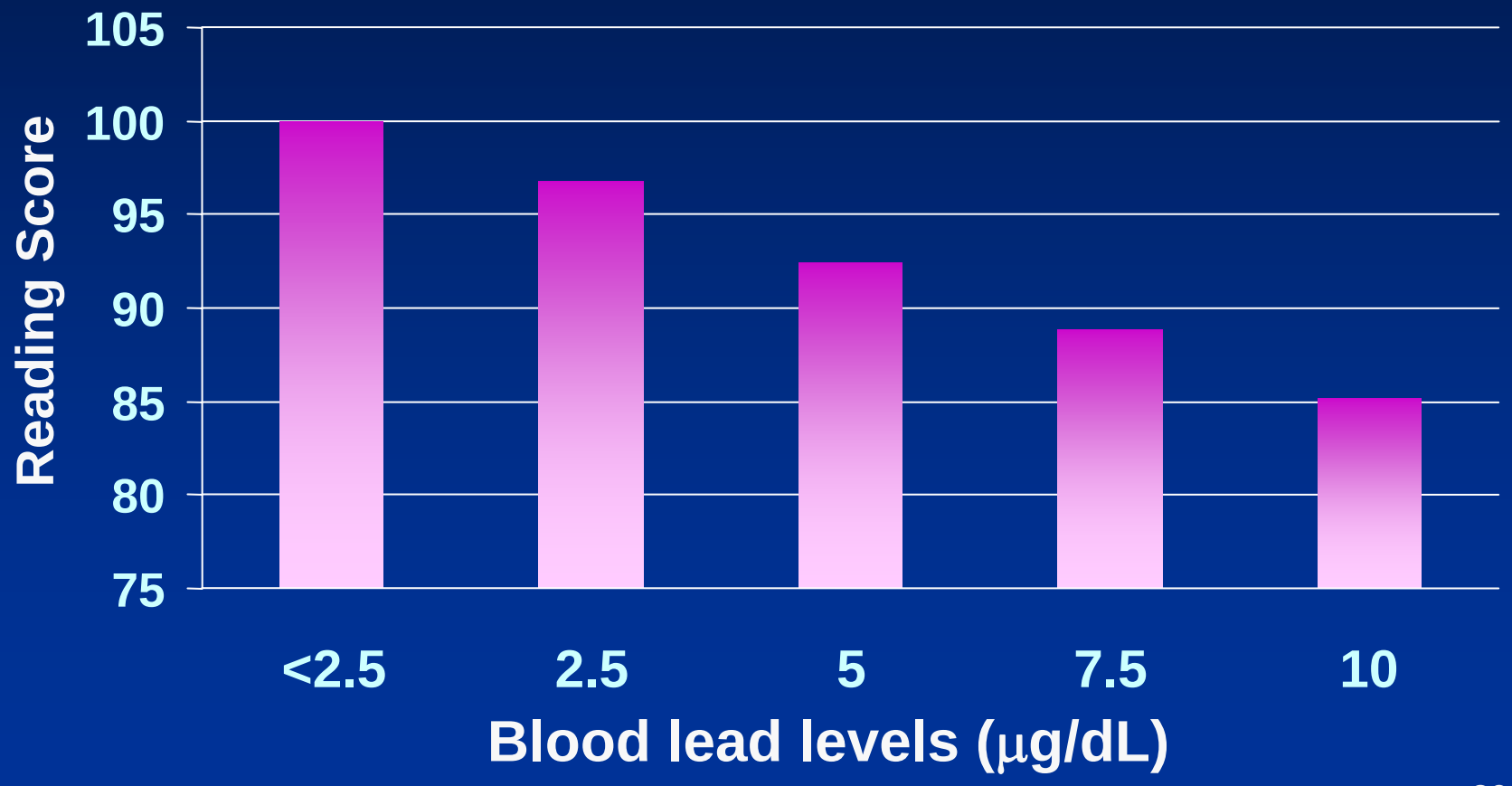
Source: CDC

Test Performance by Blood Lead



NHANES III

Mean Reading Scores by Blood Lead Concentration



NHANES III

Lead Measurement

- Blood Lead -- Short term exposure
- Bone Lead -- Long term exposure
- Lead in Environmental media
  - Sample analysis & XRF Lead Analyzer
  - Paint, Dust, Soil
  - Ambient Air
  - Other Possible Sources (food, folk remedies, ceramics, vinyl plastic)
- *Capacity to track levels key to progress*

DAY 2 TOPIC 1:

Bioequivalence Methods for Locally Acting Drugs that Treat Gastrointestinal (GI) Conditions

Bioequivalence Methods for Locally Acting Drugs That Treat Gastrointestinal (GI) Conditions

Drugs that treat gastrointestinal (GI) conditions through local action as opposed to systemic exposure will be discussed. FDA's 2007 document "Critical Path Opportunities for Generic Drugs"[1] identified development of bioequivalence methods for locally acting GI drugs as a critical path opportunity.

For these locally acting products, OGD's usual in vivo bioequivalence studies that compare pharmacokinetic parameters may not be an appropriate surrogate of pharmacological activity. This is because the systemic exposure may not be directly correlated to the local concentration of drug in the GI tract that provides clinical efficacy. Comparative clinical trials can be requested but their expense often eliminates generic competition and they are the least efficient way to detect differences in product performance (as they are relatively insensitive to these differences). Selection of the most appropriate bioequivalence method requires understanding of physicochemical properties of drugs, product design, and drug product safety and efficacy profiles.

Current FDA Recommendations

For insoluble binding agents, their therapeutic effectiveness is determined by the binding capacity of the active ingredient and the disintegration/dispersion of the active ingredient to provide local availability to the site of action. In vitro binding assays ensure that test and reference products have equivalent binding capacity. Consequently, the FDA recommended in vitro disintegration and binding assays for demonstrating bioequivalence for insoluble binding agents.

FDA has granted biowaivers for immediate release high solubility drugs that act locally in the GI tract. Products requesting biowaivers needed to show equivalent dissolution to the reference product in the physiologically relevant pH dissolution media: (a) 0.1 N HCl; (b) a pH 4.5 buffer; and (c) a pH 6.8 buffer. If the proposed drug product has a different formulation than the reference drug product, additional studies including in vivo pharmacokinetics, pharmacodynamics or clinical studies may be recommended to demonstrate that any formulation differences between proposed and reference drug products will not affect the safety and effectiveness of the drug product.

[1] http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html

Product Category	Recommendation[2]
Insoluble Binding Agents	In vitro disintegration and binding assay
High Solubility Immediate Release Dosage Forms	In vitro dissolution + studies to show that any difference in formulation does not affect the safety and efficacy of drug product
Low Solubility Immediate Release Dosage Forms	To be discussed

BE Recommendations for Low Solubility Drugs

For highly soluble drugs dosed in immediate dosage forms, the similarity of in vitro dissolution in the aqueous media of 0.1 HCl, pH 4.5 and pH 6.8 buffers ensures equivalent dissolution in vivo as these dissolution media are relatively conservative compared to in vivo conditions. However, the same dissolution media can not be used for low solubility drugs as the drugs may not completely dissolve. One possible alternative is to use biorelevant dissolution media. Over the past ten years, the utility of biorelevant dissolution in predicting in vivo dissolution and pharmacokinetics has gained recognition in the scientific community. Biorelevant dissolution is widely used in the pharmaceutical industry in predicting oral drug absorption, although its regulatory use is limited.

In addition to ensuring equivalent dissolution in vivo, the impact of any difference in formulation between test and reference products should also be considered. As result, if the proposed drug product that is not qualitatively and quantitatively the same at the reference drug product, additional studies may be recommended to show that any difference in formulation does not affect the safety and efficacy of drug product. The recommendation of these additional studies will be made on a case-by-case basis, depending on the drug and its mechanism of action.

For this advisory committee meeting, we would like the committee to comment on the following questions:

1. What role should biorelevant dissolution play in developing BE recommendations for low solubility locally acting drugs that treat GI conditions?
2. What role should systemic pharmacokinetics play in developing BE recommendation for low solubility locally acting drugs that treat GI conditions?

Presentation

1. Bioequivalence of Locally Acting GI Drugs: An Overview
   Lawrence Yu, Director for Science, Office of Generic Drugs

[2] If there is a safety concern related to systemic exposure or there are contributions of systemic exposure to efficacy, then OGD will recommend a PK study intended to demonstrate equivalent systemic exposure, in addition to any other study requested to demonstrate equivalent local delivery.

2. Why Is the In Vitro Method Better Than In Vivo?
   James Polli, Prof. of Pharmaceutical Science, University of Maryland
3. FDA OGD Considerations for Poorly Soluble Locally Acting GI Drugs
   Robert Lionberger, Ph.D., Chemical Engineer, Office of Generic Drugs

DAY 2 TOPIC 2:

Drug Classification of Orally Disintegrating Tablets (ODT)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
July 22 - 23, 2008 Meeting

Topic: Orally Disintegrating Tablets (ODT)
Prepared by: Frank O. Holcombe, Jr.

Classification of Orally Disintegrating Tablets -- Issues

Beginning in 1996, several drug products were approved as Orally Disintegrating Tablets (ODT). These early products were designed to readily and quickly disintegrate upon contact with saliva, converting the tablet to a residue or solution prior to swallowing. Based on physical differences from traditional tablets, and because this was an administration technique that had not been used previously, a new and separate dosage form was created to differentiate these from other tablet products. The dosage form definition was constructed as a balance of addressing the unique properties of the products while not restricting possible innovation for this product class. Subsequently, as the range of products claiming this dosage form increased and variation from the identifying characteristics of the initial products became greater because of extension to other drugs and development of new formulation technologies, concerns arose about whether some of the newer products could correctly be designated as an ODT. Additionally, because it is a general requirement that an abbreviated new drug (ANDA) be the same dosage form as an approved NDA, identification of what variability is acceptable for ODTs is a significant issue. Draft guidance has been prepared to address these concerns, but questions about guidance scope and criteria specificity still remain.

Draft Questions for Committee Discussion:

1. What properties (in-vivo or in-vitro) do you consider critical to this dosage form?
2. Should physical properties (e.g., size, formulation, disintegration times) be a primary factor in determining conformance to this dosage form?
    a. If so, how specific or restrictive should the criteria be?
3. Can labeling (i.e. instructions for use) be considered sufficient to define the dosage form?
    a. If so, should labeling describe/include differences between/among NDA and ANDA products?
4. Are there special issues that should be considered (e.g. patient compliance, target populations/conditions)?

Guidance for Industry
Orally Disintegrating Tablets

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Frank O. Holcombe, Jr., Ph.D., 240-276-9310.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2007
Chemistry

Guidance for Industry
Orally Disintegrating Tablets

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U.S. Department of Health and Human Services
Food and Drug Administration
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April 2007
Chemistry

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Guidance for Industry[1]
Orally Disintegrating Tablets

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides pharmaceutical manufacturers of new and generic drug products with an Agency perspective on the definition of an *orally disintegrating tablet* (ODT), which is a different dosage form than, for example, a chewable tablet or a tablet that should be swallowed whole with liquid, and also provides recommendations to applicants who would like to designate proposed products as ODTs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, pharmaceutical manufacturers have developed products that can be ingested simply by placing them on the tongue. The products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need for chewing the tablet, swallowing an intact tablet, or taking the tablet with water. This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders).

[1] This guidance was prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

After the Agency received and reviewed applications for the initial products, the CDER Nomenclature Standards Committee developed the following definition for an orally disintegrating tablet (ODT) as a new dosage form in 1998:

> *A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.*[2]

Characteristics that were exhibited by the initial products included low tablet weight, small size, highly soluble components, and rapid disintegration. Such characteristics supported the intended uses of these products.

However, as firms started developing additional products using different technology and formulations, many of these later products exhibited wide variation in product characteristics from the initial products. Because this shift in product characteristics can affect suitability for particular uses, the Agency developed this guidance for industry.

III. DISCUSSION

As briefly discussed in Section II, an ODT has previously been distinguished as a separate dosage form because of the specific, intended performance characteristics of such products, which are rapid oral disintegration in saliva with no need for chewing or drinking liquids to ingest these products. These characteristics, which are an aid to patient use and compliance, are the primary characteristics that constitute the basis for classifying a product as an ODT.

The recommendations in this guidance are based on the intention of the original definition and on Agency experience with new drug applications (NDAs) and abbreviated new drug applications (ANDAs) submitted for this dosage form. To determine what the Agency's experience has been, we surveyed applications for products submitted to the Agency, completed a literature review, and collected information from laboratory studies that showed although disintegration times ranged from a few seconds to longer than a minute, a large majority of these products have in-vitro disintegration times of approximately 30 seconds or less. These products represented different manufacturing technologies, a variety of tablet sizes and weights, and various disintegration strategies demonstrating that relatively rapid disintegration is readily achievable across a variety of products.

Products labeled as ODTs should match the characteristics for this dosage form (rapid disintegration in saliva without need for chewing or drinking liquids). Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative (see section IV).

[2] CDER Data Standards Manual

Although the value of 30 seconds is given as a desired result, it is not intended to represent an arbitrary distinction between an ODT and some other tablet form. It is instead representative of a general time period associated with drug products that have been found to have performance characteristics appropriate for a disintegrating tablet meant to be taken without chewing or liquids.

We recommend that as a primary consideration when developing this type of product you use the defining characteristics for this dosage form designation (rapid disintegration in saliva without need for chewing or liquids). Products should be developed to match these characteristics, rather than labeling a tablet as an ODT because it would eventually disintegrate when placed in the mouth. For example, tablets that take longer than 30 seconds to disintegrate or are dosed with liquids may be more appropriately considered to be chewable or oral tablets.

Additional parameters for consideration during product development are tablet size, weight, component solubility, and the effect these factors have on the intended use of the product. While tablet size or weight is not explicitly included in the definition, you should consider the effect large tablets have on patient safety and compliance. We recommend that the weight of the tablet not exceed 500 mg. If it does, the extent of component solubility (e.g., tablet residue, need for liquids) can influence the acceptability of a large tablet being labeled as an ODT.

IV. DISINTEGRATION TESTING

Part of the process of determining if a product is an ODT involves testing a product to see how long it takes to disintegrate. Determination of disintegration time appears to be method dependent. There are many methods—some more discriminating than others. To provide both a standard for and consistency in disintegration testing, we recommend that applicants use the USP method for disintegration testing.[3] However, other methods that can be correlated with or are demonstrated to provide results equivalent to the USP method can also be used and submitted to determine disintegration time.

[3] *USP 29, <701> Disintegration*, pp 2670-2672.

DAY 2 TOPIC 3:

Use of Inhaled Corticosteroid Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products

Use of Inhaled Corticosteroid Dose-response as a Means to Establish Bioequivalence of Inhalation Drug Products

Establishing bioequivalence (BE) of inhaled corticosteroids (ICS) requires a study design that is sensitive to dose differences. Published dose-response and potency studies have utilized parallel designs for evaluation of ICS response. Parallel designs were used to circumvent the carryover effect between treatments that prevented use of crossover studies. However, experience shows that for ICS, parallel designs generally lack sensitivity to distinguish differences in potency (i.e., little or no dose-response at the labeled dose and multiples thereof), and possess high variability. Based on parallel design studies, the estimated sample size for documentation of BE is 1000 subjects or more.

At present, no validated methods with acceptable sensitivity and precision are available for ICS. In 2001, Richard Ahrens,[1] University of Iowa, proposed a novel clinical model ("asthma stability model") for determining relative potency of ICS using a crossover study design in asthmatic subjects, in which the subjects serve as their own controls, thus increasing study power. The study is unique in using a wash-in of high dose corticosteroid to equalize carryover between treatment periods, thus allowing a crossover design. Based on pilot study data using the asthma stability model, the number of subjects needed for a relative potency or BE study is estimated to be fewer than 100, an order of magnitude lower than the number needed in a parallel design. The improved study power results in a study design that appears practical to establish BE. Therefore, FDA has sponsored a pilot study to examine this model for determining relative potency or BE of inhaled corticosteroids using a wash-in of high dose steroid to equalize carryover between treatment periods, thus allowing a crossover design and potentially reducing dramatically the number of subjects.

The asthma stability model uses FEV_1 as the pharmacodynamic endpoint. An alternative study design is based on exhaled nitric oxide (eNO), a marker of airway inflammation. Asthmatic patients exhale elevated levels of NO due to the inflammatory nature of the disease. Dosing with ICS decreases eNO levels, and this reduction exhibits a dose-response.[2,3] The magnitude of dose-response may be substantially greater than that observed with FEV_1 as an endpoint. eNO studies do not require dosing to a plateau with high dose corticosteroid, as is done with the asthma stability model - an advantage in decreasing subject exposure to corticosteroids.

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[1] RC Ahrens, ME Teresi, S-H Han et al., "Asthma stability after oral prednisone: A clinical model for comparing inhaled steroid potency." *Am J Respir Crit Care Med* 2001;164:1138-45

[2] PE Silkoff, P McClean, M Spino et al, "Dose-response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients." *Chest* 2001;119:1322-8.

[3] AM Wilson, BJ Lipworth, "Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma." *Am J Med,* 2000;108:269-75.

A major benefit of a BE study based on an eNO endpoint is that eNO levels appear to be unaffected by concomitant administration of beta-agonists.[4,5] This characteristic suggests that bioequivalence of combination drug products consisting of both an ICS and a long-acting beta-agonist may be established using FEV_1 (bronchodilatation or bronchoprovocation) for the beta-agonist component and eNO for the ICS component of the drug. In terms of time interval between study treatments, a two week washout period between treatments may be adequate to restore eNO baseline to allow crossover studies. This compares with the approximately two week wash-in to attain the plateau of response in the asthma stability model. However, the treatment arms for determination of dose-response using eNO may be of shorter (1-3 week) duration, compared with 4-6 weeks for the asthma stability model.

The FDA is funding two studies, one based on the asthma stability model, and one based on the eNO model, to investigate the potential of each study to produce substantial dose-response curves that may be suitable for establishing bioequivalence of ICS based on a pharmacodynamic endpoint.

The purpose of this meeting is to update ACPS OGD's effort in developing bioequivalence methods for inhaled corticosteroids. In the future, OGD will present research outcomes and possibly bioequivalence method recommendations for inhaled corticosteroids

1. Bioequivalence of Inhalation Drug Products: Challenges and Opportunities
   Lawrence Yu, Director for Science, Office of Generic Drugs
2. Asthma Stability Model for Inhaled Corticosteroid Dose-response
   Wallace Adams, Leading Pharmacologist, FDA
3. Exhaled Nitric Oxide Study Model for Inhaled Corticosteroid Dose-response
   Badrul Chowdhury, Director, Division of Pulmonary and Allergy Drug Products, FDA

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[4] DKC Lee, CM Jackson, GP Currie et al, "Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma." *Br J Clin Pharmacol* 2003;56:494-500.

[5] L Prieto, V Gutierrez, C Perez-Frances et al, "Effect of fluticasone propionate-salmeterol therapy on seasonal changes in airway responsiveness and exhaled nitric oxide levels in patients with pollen-induced asthma." *Ann Allergy Asthma Immunol* 2005;95:452-61

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Advisory Committee for Pharmaceutical Science
and
Clinical Pharmacology
July 22-23, 2008

Day 1: Tuesday, July 22, 2008

Lead in Pharmaceutical Products

1. Kauffman, J. F., Westenberger, B. J., et. al., "Lead in pharmaceutical products and dietary supplements", *Regulatory Toxicology and Pharmacology*, vol. 48, (2007): 128-134.

Day 2: Wednesday, July 23, 2008

Bioequivalence Methods for Locally Acting Drugs that Treat Gastrointestinal (GI) Conditions

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2. Silkoff, P.E., McClean, P., et. al., "Dose-response Relationship and Reproducibility of the Fall in Exhaled Nitric Oxide after Inhaled Beclomethatsone Dipropionate Therapy in Asthma Patients", *CHEST*, vol. 119, (2001): 1322-1328.

3. Wilson, A.M. and Lipworth, B., "Dose-response Evaluation of the Therapeutic Index for Inhaled Budesonide in Patients with Mild-to-Moderate Asthma", *The American Journal of Medicine*, vol. 108 (2000): 269-275.

4. Lee, D.K.C., Jackson, C.M., et. al., "Comparison of Combination Inhalers vs. Inhaled Corticosteroids Alone in Moderate Persistent Asthma", *Journal of Clinical Pharmacology*, vol. 56, (2003): 494-500.

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